CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091632

Name: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension (equivalent to 10 mg Hydrocodone Bitartrate and 8 mg Chlorpheniramine Maleate per 5 mL)

Sponsor: Tris Pharma, Inc.

Approval Date: October 1, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091632

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs and Compliance
2033 Route 130, Suite D
Monmouth Junction, NJ 08852

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 13, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, (equivalent to 10 mg Hydrocodone Bitartrate and 8 mg Chlorpheniramine Maleate per 5 mL).

Reference is also made to your amendments dated November 17, 2009; and March 4, March 16, April 28, May 24, May 25, July 1, July 19, September 10, September 14, and September 24, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Tussionex Pennkinetic Extended-release Oral Suspension, of UCB, Inc.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Dissolution Testing should be conducted using:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCl for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5°C
Sampling Time: 1, 3, 6 and 12 hours

Specifications:

Time (Hours)	Hydrocodone (Percent Dissolved)	Chlorpheniramine (Percent Dissolved)
1	(b) (4)	(b) (4)
3		
6		
12		

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with

applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

10/01/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

LABELING

Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension

Rx Only

LB8072 Rev 00 11/09

Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension

Rx Only

CIII

HYDROCODONE POLISTIREX AND CHLORPHENIRAMINE POLISTIREX EXTENDED RELEASE ORAL SUSPENSION
10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

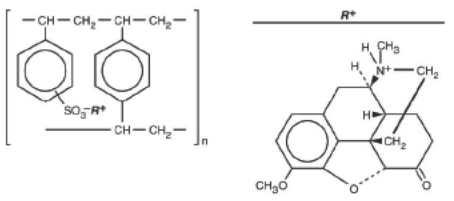
Rx Only

DESCRIPTION

Each teaspoonful (5 mL) of hydrocodone polistirex and chlorpheniramine polistirex extended release (ER) oral suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is for oral use only.

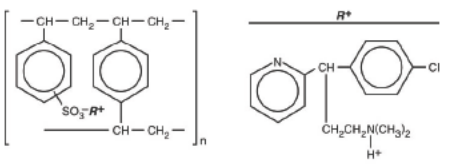
Hydrocodone Polistirex

Sulfonated styrene-divinylbenzene copolymer complex with 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one.



Chlorpheniramine Polistirex

Sulfonated styrene-divinylbenzene copolymer complex with 2-[p-chloro-α-[2-(dimethylamino)ethyl]-benzyl]pyridine.



Inactive Ingredients

Ascorbic acid, D&C Yellow No. 10, flavors, high fructose corn syrup, modified food starch, methylparaben, polysorbate 80, polyvinyl acetate, propylene glycol, propylparaben, purified water, sodium ascorbate, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, xanthan gum.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic antitussive and analgesic with multiple actions qualitatively similar to those of codeine. The precise mechanism of action of hydrocodone and other opiates is not known; however, hydrocodone is believed to act directly on the cough center. In excessive doses, hydrocodone, like other opium derivatives, will depress respiration. The effects of hydrocodone in therapeutic doses on the cardiovascular system are insignificant. Hydrocodone can produce miosis, euphoria, and physical and psychological dependence.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic and sedative activity. It prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Hydrocodone release from hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is controlled by an extended-release drug delivery system, which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Following multiple dosing with hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension, hydrocodone mean (S.D.) peak plasma concentrations of 22.8 (5.9) ng/mL occurred at 3.4 hours. Chlorpheniramine mean (S.D.) peak plasma concentrations of 58.4 (14.7) ng/mL occurred at 6.3 hours following multiple dosing. Peak plasma levels obtained with an immediate-release syrup occurred at approximately 1.5 hours for hydrocodone and 2.8 hours for chlorpheniramine. The plasma half-lives of hydrocodone and chlorpheniramine have been reported to be approximately 4 and 16 hours, respectively.

INDICATIONS AND USAGE

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.

CONTRAINDICATIONS

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is contraindicated in patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine.

The use of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

WARNINGS

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Respiratory Depression

As with all narcotics, hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm and may produce irregular and periodic breathing. Caution should be exercised when hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is used postoperatively and in patients with pulmonary disease, or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated (see OVERDOSAGE).

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions, which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions

The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Obstructive Bowel Disease

Chronic use of narcotics may result in obstructive bowel disease especially in patients with underlying intestinal motility disorder.

Pediatric Use

The use of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is contraindicated in children less than 6 years of age (see CONTRAINDICATIONS).

In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Caution should be exercised when administering hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension to pediatric patients 6 years of age and older. Overdose or concomitant administration of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension with other respiratory depressants may increase the risk of respiratory depression in pediatric patients. Benefit to risk ratio should be carefully considered, especially in pediatric patients with respiratory embarrassment (e.g., croup) (see PRECAUTIONS).

PRECAUTIONS

General

Caution is advised when prescribing this drug to patients with narrow-angle glaucoma, asthma, or prostatic hypertrophy.

Special Risk Patients

As with any narcotic agent, hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients

As with all narcotics, hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension may produce marked drowsiness and impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension must not be diluted with fluids or mixed with other drugs as this may alter the resin-binding and change the absorption rate, possibly increasing the toxicity.

Patients should be advised to measure hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when a half a teaspoon is measured. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.

Shake well before using.

Keep out of the reach of children.

Cough Reflex

Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is used postoperatively, and in patients with pulmonary disease.

Drug Interactions

Patients receiving narcotics, antihistaminics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension.

Pregnancy

Teratogenic Effects – Pregnancy Category C

Hydrocodone has been shown to be teratogenic in hamsters when given in doses 700 times the human dose. There are no adequate and well-controlled studies in pregnant women. Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose.

Labor and Delivery

As with all narcotics, administration of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The use of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is contraindicated in children less than 6 years of age (see CONTRAINDICATIONS and ADVERSE REACTIONS, Respiratory, Thoracic and Mediastinal Disorders).

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension should be used with caution in pediatric patients 6 years of age and

older (see WARNINGS, Pediatric Use).

Geriatric Use

Clinical studies of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Gastrointestinal Disorders

Nausea and vomiting may occur; they are more frequent in ambulatory than in recumbent patients. Prolonged administration of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension may produce constipation.

General Disorders and Administration Site Conditions

Death

Nervous System Disorders

Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.

Renal and Urinary Disorders

Ureteral spasm, spasm of vesical sphincters, and urinary retention have been reported with opiates.

Respiratory, Thoracic and Mediastinal Disorders

Dryness of the pharynx, occasional tightness of the chest, and respiratory depression (see CONTRAINDICATIONS).

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE). Use of hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension in children less than 6 years of age has been associated with fatal respiratory depression. Overdose with hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension in children 6 years of age and older, in adolescents, and in adults has been associated with fatal respiratory depression.

Skin and Subcutaneous Tissue Disorders

Rash, pruritus.

DRUG ABUSE AND DEPENDENCE

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is a Schedule III narcotic. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of narcotics; therefore, hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is used for a short time for the treatment of cough. Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued oral narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy.

OVERDOSAGE

Signs and Symptoms

Serious overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdosage apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdosage may vary from central nervous system depression to stimulation.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote for respiratory depression which may result from overdosage or unusual sensitivity to narcotics including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of hydrocodone in this formulation may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. For further information, see full prescribing information for naloxone hydrochloride. An antagonist should not be administered in the absence of clinically significant respiratory depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

It is important that hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension is measured with an accurate measuring device (see PRECAUTIONS, Information for Patients). A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate measuring device and can provide instructions for measuring the correct dose.

Shake well before using.

Adults and Children 12 Years and Older

5 mL (1 teaspoonful) every 12 hours; do not exceed 10 mL (2 teaspoonfuls) in 24 hours.

Children 6 to 11 Years of Age

2.5 mL (½ teaspoonful) every 12 hours; do not exceed 5 mL (1 teaspoonful) in 24 hours.

This medicine is contraindicated in children under 6 years of age (see CONTRAINDICATIONS).

HOW SUPPLIED

Hydrocodone polistirex and chlorpheniramine polistirex ER oral suspension, equivalent to 10 mg of hydrocodone bitartrate and 8 mg of chlorpheniramine maleate per 5 mL is a yellow viscous suspension.

NDC 27808-021-01 473 mL bottle

Storage:

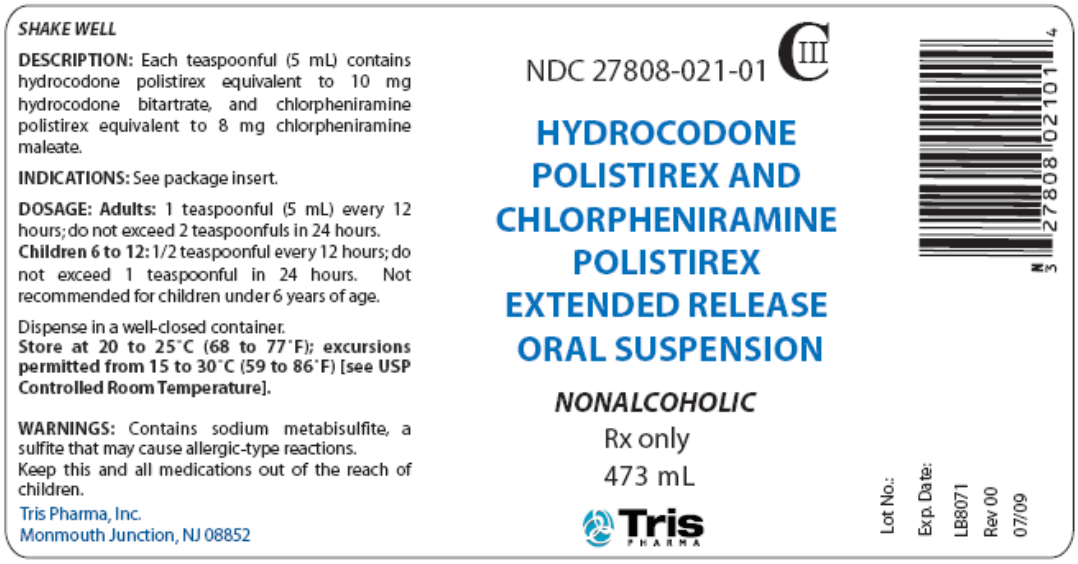
Shake well. Dispense in a well-closed container.

Store at 20 to 25°C (68 to 77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Manufactured by
Tris Pharma, Inc.
Monmouth Junction, NJ 08852

LB8072
Rev 00
11/09

1.14.2.1 Final Container Label



SHAKE WELL

DESCRIPTION: Each teaspoonful (5 mL) contains hydrocodone polistirex equivalent to 10 mg hydrocodone bitartrate, and chlorpheniramine polistirex equivalent to 8 mg chlorpheniramine maleate.

INDICATIONS: See package insert.

DOSAGE: Adults: 1 teaspoonful (5 mL) every 12 hours; do not exceed 2 teaspoonfuls in 24 hours. **Children 6 to 12:** 1/2 teaspoonful every 12 hours; do not exceed 1 teaspoonful in 24 hours. Not recommended for children under 6 years of age.

Dispense in a well-closed container.
Store at 20 to 25°C (68 to 77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

WARNINGS: Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions.
Keep this and all medications out of the reach of children.

Tris Pharma, Inc.
Monmouth Junction, NJ 08852

NDC 27808-021-01 CIII

HYDROCODONE POLISTIREX AND CHLORPHENIRAMINE POLISTIREX EXTENDED RELEASE ORAL SUSPENSION

NONALCOHOLIC

Rx only

473 mL

Tris PHARMA

N 3 27808 02101 4

Lot No.: LB8071
Exp. Date: Rev 00 07/09

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091632 Date of Submission: July 13, 2009

Applicant's Name: Tris Pharma, Inc.

Established Name: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended- Release Oral Suspension

Hydrocodone Polistirex equivalent to**10 mg** hydrocodone bitartrate and Chlorpheniramine Polistirex equivalent to **8 mg** chlorpheniramine maleate per 5 mL

Proposed Proprietary Name: None

Labeling Deficiencies:

A. CONTAINER (473 mL bottles)
Satisfactory in FPL as of July 13, 2009 e-submission

D. PACKAGE OUTSERT
HOW SUPPLIED: Clarify the strength in terms of hydrocodone bitartrate and chlorpheniramine maleate where referenced in this section.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY

A. CONTAINER LABELS (Bottles of 473 mL)
Satisfactory in FPL as of July 13, 2009 e-submission

B. PACKAGE OUTSERT
Satisfactory in FPL as of (date) e-submission

Revisions needed post-approval:

REFRENCE LISTED DRUG
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Tussionex Pennkinetic Exended-release Oral Suspension
NDA Number: NDA 019111
NDA Drug Name: Tussionex Pennkinetic (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Exended-release Suspension
NDA Firm: UCB, Inc.
Date of Approval of NDA Insert and supplement #: NDA 019111/S-015, approved March 11, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Package Outsert: side-by-side

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Tussionex® Pennkinetic® (hydrocodone polistirex/chlorpheniramine polistirex) Extended-Release Suspension (NDA 019111/S-015, approved March 11, 2008).

2. PATENTS/EXCLUSIVITIES

   There are no unexpired patents and exclusivities.

3. MANUFACTURING FACILITY

   Tris Pharma, Inc.
   2033 Route 130
   Monmouth Junction, NJ 08852

4. STORAGE CONDITIONS

   USP: None.
   RLD: Store at 15°-30°C (59°-86°F).
   ANDA: Store at 20° to 25°C (68°to 77°F); excursion permitted from 15° to 30°C (59°to 86°F) [See USP Controlled Room Temperature.]

5. DISPENSING RECOMMENDATIONS

   USP: None
   RLD: Dispense in a well-closed container.
   ANDA: Dispense in a well-closed container.

6. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling does appear accurate according to the components and composition statement.

Ingredients	Function	Quantity (mg/5 mL)
Sodium Polystyrene Sulfonate (b) (4)	(b) (4)	
Hydrocodone Bitartrate USP	Active	10
Chlorpheniramine Maleate USP	Active	8
Purified Water USP		(b) (4)
Polyvinyl Acetate (b) (4)		
(b) (4)		
Triacetin USP		
Sodium Metabisulfite NF (b) (4)		
Polysorbate 80 NF (b) (4)		
Propylene Glycol USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF (b) (4)		

Ascorbic Acid USP
Sodium Ascorbate USP
High Fructose Corn Syrup [redacted]
Sucrose NF
D&C Yellow No. 10
[redacted](Food Starch – Modified)
[redacted]Flavor [redacted]

[redacted]

7. PACKAGING CONFIGURATIONS

RLD: Bottles of 473 mL
ANDA: Bottles of 473 mL

8. CONTAINER/CLOSURE

The drug product Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL test batch, TB-047A, was packaged in a 16 oz (473 mL) [redacted]Clear Glass [redacted]Round Container with smooth top closure.

Item	Description	Quantity per Unit	Comments
1	Clear, colorless to slightly yellow solution.	473 mL	--
2	Container, 16 oz. [redacted]Clear Glass [redacted]Round Container [redacted]	1	--
3	Closure, 28mm [redacted]White [redacted] Smooth Top Closure [redacted]	1	--
4	Container Label	1	--
5	Outsert	1	On top of closure
6	Neck Band	1	--

9. PRODUCT DESCRIPTION

Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL is described in the HOW SUPPLIED section as a yellow viscous suspension.

10. NAME & ADDRESS OF APPLICANT

Name:	Tris Pharma, Inc.
Address:	2033 Route 130 Monmouht Junction, NJ 08852
Representative:	W. Scott Groner Director, Regulatory Affairs and Compliance
Telephone:	Tel: (732) 940-0358
Fax:	Fax: (732) 940-0374

Date of Review: November 2, 2009

Date of Submission: July 13, 2009

Primary Reviewer: Burhan Nour

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BURHAN A NOUR
11/03/2009

JOHN F GRACE
11/09/2009

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091632 Date of Submission: November 17, 2009

Applicant's Name: Tris Pharma, Inc.

Established Name: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended- Release Oral Suspension

Hydrocodone Polistirex equivalent to**10 mg** hydrocodone bitartrate and Chlorpheniramine Polistirex equivalent to **8 mg** chlorpheniramine maleate per 5 mL

Proposed Proprietary Name: None

BASIS OF APPROVAL:

APPROVAL SUMMARY

A. CONTAINER LABELS (Bottles of 473 mL)
Satisfactory in FPL as of July 13, 2009 e-submission

B. PACKAGE OUTSERT
Satisfactory in FPL as of November 17, 2009 e-submission

Revisions needed post-approval:

REFRENCE LISTED DRUG
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Tussionex Pennkinetic Exended-release Oral Suspension
NDA Number: NDA 019111
NDA Drug Name: Tussionex Pennkinetic (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Exended-release Suspension
NDA Firm: UCB, Inc.
Date of Approval of NDA Insert and supplement #: NDA 019111/S-015, approved March 11, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Package Outsert: side-by-side

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Tussionex® Pennkinetic® (hydrocodone polistirex/chlorpheniramine polistirex) Extended-Release Suspension (NDA 019111/S-015, approved March 11, 2008).

2. PATENTS/EXCLUSIVITIES

   There are no unexpired patents and exclusivities.

3. MANUFACTURING FACILITY

   Tris Pharma, Inc.
   2033 Route 130
   Monmouth Junction, NJ 08852

4. STORAGE CONDITIONS

   USP: None.
   RLD: Store at 15°-30°C (59°-86°F).
   ANDA: Store at 20° to 25°C (68°to 77°F); excursion permitted from 15° to 30°C (59°to 86°F) [See USP Controlled Room Temperature.]

5. DISPENSING RECOMMENDATIONS

   USP: None
   RLD: Dispense in a well-closed container.
   ANDA: Dispense in a well-closed container.

6. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling does appear accurate according to the components and composition statement.

Ingredients	Function	Quantity (mg/5 mL)
Sodium Polystyrene Sulfonate (b) (4)	(b) (4)	
Hydrocodone Bitartrate USP	Active	10
Chlorpheniramine Maleate USP	Active	8
Purified Water USP		(b) (4)
Polyvinyl Acetate (b) (4)		
(b) (4)		
Triacetin USP		
Sodium Metabisulfite NF (b) (4)		
Polysorbate 80 NF (b) (4)		
Propylene Glycol USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF (b) (4)		

Ascorbic Acid USP
Sodium Ascorbate USP
High Fructose Corn Syrup [redacted]
[redacted]
Sucrose NF
D&C Yellow No. 10
[redacted](Food Starch – Modified)
[redacted]Flavor [redacted]
[redacted]

[redacted]

7. PACKAGING CONFIGURATIONS

RLD: Bottles of 473 mL
ANDA: Bottles of 473 mL

8. CONTAINER/CLOSURE

The drug product Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL test batch, TB-047A, was packaged in a 16 oz (473 mL) [redacted]Clear Glass [redacted]Round Container with smooth top closure.

Item	Description	Quantity per Unit	Comments
1	Clear, colorless to slightly yellow solution.	473 mL	--
2	Container, 16 oz. [redacted]Clear Glass [redacted]Round Container [redacted]	1	--
3	Closure, 28mm-[redacted]White, [redacted] Smooth Top Closure [redacted]	1	--
4	Container Label	1	--
5	Outsert	1	On top of closure
6	Neck Band	1	--

9. PRODUCT DESCRIPTION

Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL is described in the HOW SUPPLIED section as a yellow viscous suspension.

10. NAME & ADDRESS OF APPLICANT

Name:	Tris Pharma, Inc.
Address:	2033 Route 130 Monmouht Junction, NJ 08852
Representative:	W. Scott Groner Director, Regulatory Affairs and Compliance
Telephone:	Tel: (732) 940-0358
Fax:	Fax: (732) 940-0374

11. SPL

HYDROCODONE POLISTIREX AND CHLORPHENIRAMINE POLISITREX
hydrocodone bitartrate and chlorpheniramine maleate suspension, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	NDC Product Code (Source)	27808-021
Route of Administration	ORAL	DEA Schedule	CIII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCODONE BITARTRATE (HYDROCODONE)	HYDROCODONE BITARTRATE	10 mg in 5 mL
CHLORPHENIRAMINE MALEATE (CHLORPHENIRAMINE)	CHLORPHENIRAMINE MALEATE	8 mg in 5 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM POLYSTYRENE SULFONATE	
WATER	
VINYL ACETATE	
TRIACETIN	
SODIUM METABISULFITE	
POLYSORBATE 80	
PROPYLENE GLYCOL	
METHYLPARABEN	
PROPYLPARABEN	
XANTHAN GUM	
ASCORBIC ACID	
SODIUM ASCORBATE	
HIGH FRUCTOSE CORN SYRUP	
SUCROSE	
D&C YELLOW NO. 10	
MODIFIED (b) (4) **STARCH** (b) (4)	

Product Characteristics

Color	YELLOW	Score	
Shape		Size	
Flavor	(b) (4)	Imprint Code	

Contains

Packaging

#	NDC	Package Description	Multilevel Packaging
1	27808-021-01	473 mL In 1 BOTTLE, GLASS	None

Date of Review: November 20, 2009

Date of Submission: November 17, 2009

Primary Reviewer: Burhan Nour

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BURHAN A NOUR
11/23/2009

JOHN F GRACE
11/30/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

CHEMISTRY REVIEWS

ANDA 091632

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension (Equivalent to 10 mg Hydrocodone Bitartrate and 8 mg Chlorpheniramine Maleate per 5 mL)

Tris Pharma Inc.

Gil-Jong Kang
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 091632

-

2. REVIEW #: 1

3. REVIEW DATE: 25-JAN-2010, revised 18-FEB-2010

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-JUL-2009
Refuse to receive	13-AUG-2009
Amendment	26-AUG-2009
Date (received) acceptable for filing	27-AUG-2009
Consult request (Sodium ascorbate)	28-AUG-2009
Expedited review granted	18-SEP-2009
Consult result (Sodium ascorbate)	01-OCT-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Tris Pharma, Inc.
Address:	2033 Route 130 Monmouth Junction, NJ 08852
Representative:	W. Scott Groner
Telephone: Fax:	(732) 940-0358 (732) 940-0374

8. DRUG PRODUCT NAME:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug: Tussionex® Pennkinetic®
Manufactured by UCB Inc.

Application Number: N019111

Strength: 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

Patent Certification: No unexpired patents for this product.

Exclusivity: None

10. PHARMACOL. CATEGORY:

Relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.

11. DOSAGE FORM:

Extended-Release Oral Suspension

12. STRENGTH/POTENCY:

10 mg Hydrocodone bitartrate and 8 mg Chlorpheniramine maleate per 5 mL

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

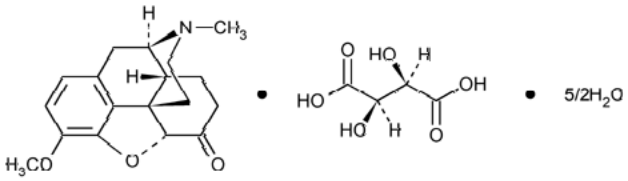
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Hydrocodone Bitartrate:

4,5α -Epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1) hydrate (2:5)

($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 5/2\ H_2O$, MW = 494.50)

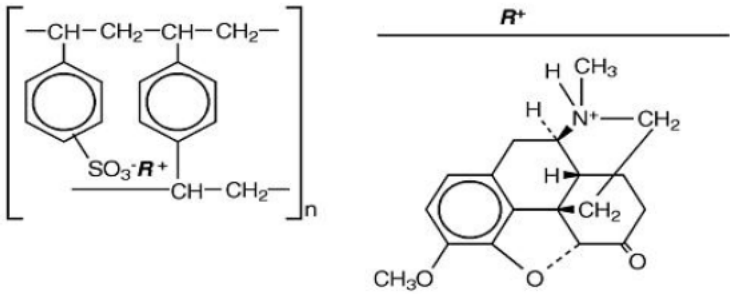
CAS#: 34195-34-1



Hydrocodone Polistirex

Molecular Formula: $C_{18}H_{21}NO_3$ (hydrocodone)

Molecular Weight: 299.35 (hydrocodone)

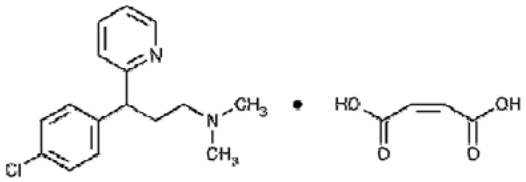


Chlorpheniramine Maleate:

2-[p-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1)

($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, MW = 390.86)

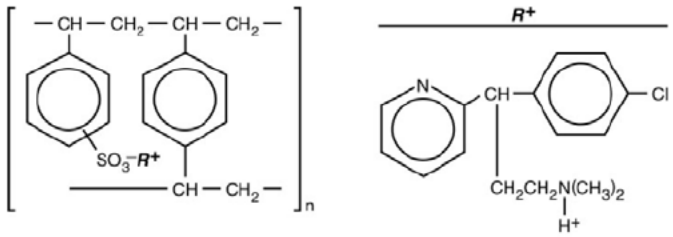
CAS#: [113-92-8]



Chlorpheniramine Polistirex

Molecular Formula: $C_{16}H_{19}ClN_2$ (chlorpheniramine)

Molecular Weight: 274.80 (chlorpheniramine)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	08-JUN-2009	Reviewed by Q. Zhang.
	II			3	Adequate	29-APR-2009	Reviewed by G. Sun.
	II			4			
	IV			4			
	V			4			
	IV			4			(b) (4)
	IV			4			
	III			4			
	III			4			
	III			4			Meets the USP <660> test.
	IV			4			
	III			4			FDA 21 CFR 177.1210

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	**Pending**		
Methods Validation	N/A		
Labeling	acceptable	30-NOV-2009	B. Nour
Bioequivalence	Dissolution: pending BE studies: **Pending**		
EA	Waiver submitted		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 091632

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor).

CMC section is deficient.
Bio section is pending.
Labeling section is acceptable.
EES is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Tussionex Pennkinetic Extended-release Oral Suspension UCB Inc.

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension is for oral use only.
Hydrocodone release from Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension is controlled extended-release drug delivery system, which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Inactive ingredients of the drug product are: Ascorbic acid, D&C Yellow No. 10, flavors, high fructose corn syrup, modified food starch, methylparaben, polysorbate 80, polyvinyl acetate, propylene glycol, propylparaben, purified water, sodium ascorbate, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, xanthan gum.

Drug product is manufactured by (b) (4) .

The processes and equipments used to manufacture the exhibit batch are functionally equivalent to the processes and equipments proposed to use in the scale-up batch.

The exhibit batches were packaged using (b) (4) placed on stability according their stability protocol. The firm submitted three months accelerated and room temperature stability data.
The firm has requested 24 months expiration date based on the three months accelerated stability data.

B. Description of How the Drug Product is Intended to be Used

Maximum Daily Dose is 2 x 5 mL as per Labeling insert information.

Hydrocodone bitartrate: 20 mg
Chlorpheniramine maleate: 16 mg

The drug substance: based on the ICH Guideline Q3A (R)
IT is 0.10% for any single unknown impurities (unspecified).
QT is 0.15% for any specified identified or specified unidentified impurity.

The drug product: based on the ICH Guideline Q3B (R)
IT is 0.2% for any single unknown impurities (unspecified).
QT is 0.5% for any specified identified or specified unidentified impurity.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry deficiencies are related to the drug substance control, in-process control, drug product and stability specifications.
Chemistry section is not recommended for approval (Minor amendment).

Labeling section is acceptable.
Bio section is pending.
EES is pending.

Following this page, 53 pages withheld in full (b)(4)

(b) (4)

[redacted]

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion:

A waiver is provide in Section 1.12.14.

III. List Of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091632 APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide (b) (4)
2. Please comment (b) (4)
3. Please provide (b) (4)
4. (b) (4)
5.
6.

(b) (4)

7. (b) (4)

8.

9.

10. Please add (b) (4).

11. Please add (b) (4)
.

12. (b) (4)
.

13. Finished product release specification should include USP <467> residual solvents compliance statement along with option used.

14. Please revise (b) (4)

15. Please explain (b) (4).

16. (b) (4)
.

17. [redacted] (b) (4)

18. Authorization letter to refer to [redacted] (b) (4) . Please clarify.

19. Please add [redacted] (b) (4)

20. It is note in Module 3.2.P.8.1 that the containers were placed in the **horizontal position**; so that all sides of the container and the closure liner are in contact with the drug product. Please include the sample orientation in three months accelerated and on-going room temperature stability data. Also revise the stability protocol to include the orientation of stability samples.

21. [redacted] (b) (4)

22. Please clarify the storage condition of the following statement for "Expiration dating period" in Module 3.2.P.8.1. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence section of your application is under review and you will be notified separately of any deficiencies.

2. A satisfactory compliance evaluation for each of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

3. Vendor qualification for reduced testing is a cGMP issue per 21 CFR211.84 and should be discussed with the field inspectors.

4. Please provide all available updated drug product controlled room temperature stability data for our evaluation.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 091632
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G. Kang, Ph.D./2-19-10

HFD-630/S. H. Liu, Ph.D., Team Leader/2-22-10

HFD-617/S. Nguyen, Pharm.D., PM/2-24-10

F/T by : SN 2/24/10

V:\Chemistry Division III\Team 4\ANDA REVIEWS\Gil\91632RV1.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
02/24/2010

SARAH K NGUYEN
02/24/2010

SHING HOU H LIU
02/25/2010

ANDA 091632

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension

(Equivalent to 10 mg Hydrocodone Bitartrate and 8 mg Chlorpheniramine Maleate per 5 mL)

Tris Pharma Inc.

Gil-Jong Kang
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 091632

2. REVIEW #: 2

3. REVIEW DATE: 30-JUL-2010

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Refuse to receive Amendment Date (received) acceptable for filing	13-JUL-2009 13-AUG-2009 26-AUG-2009 27-AUG-2009
Consult request (Sodium ascorbate) Expedited review granted Consult result (Sodium ascorbate)	28-AUG-2009 18-SEP-2009 01-OCT-2009
Deficiency letter based on review #1	25-FEB-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor amendment	16-MAR-2010
Amendment (Dissolution specification change)	25-MAY-2010
Telephone amendment	01-JUL-2010
Telephone amendment	19-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Tris Pharma, Inc.
Address:	2033 Route 130 Monmouth Junction, NJ 08852
Representative:	W. Scott Groner

Telephone:	(732) 940-0358
Fax:	(732) 940-0374

8. DRUG PRODUCT NAME:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:

Reference listed drug: Tussionex® Pennkinetic®
Manufactured by UCB Inc.

Application Number: N019111

Strength: 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

Patent Certification: No unexpired patents for this product.

Exclusivity: None

10. PHARMACOL. CATEGORY:

Relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.

11. DOSAGE FORM:

Extended-Release Oral Suspension

12. STRENGTH/POTENCY:

10 mg Hydrocodone bitartrate and 8 mg Chlorpheniramine maleate per 5 mL

13. ROUTE OF ADMINISTRATION:

Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

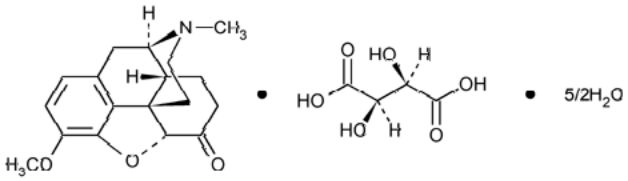
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Hydrocodone Bitartrate:

4,5α -Epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1) hydrate (2:5)

($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 5/2\ H_2O$, MW = 494.50)

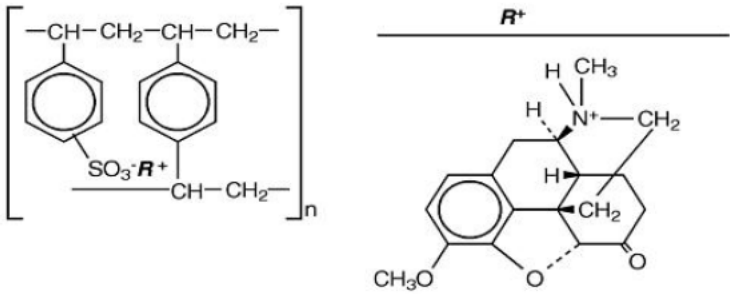
CAS#: 34195-34-1



Hydrocodone Polistirex

Molecular Formula: $C_{18}H_{21}NO_3$ (hydrocodone)

Molecular Weight: 299.35 (hydrocodone)

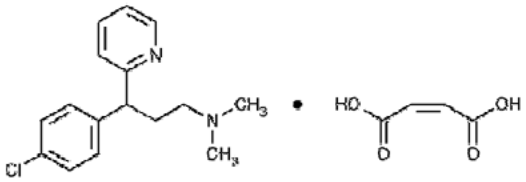


Chlorpheniramine Maleate:

2-[p-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1)

($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, MW = 390.86)

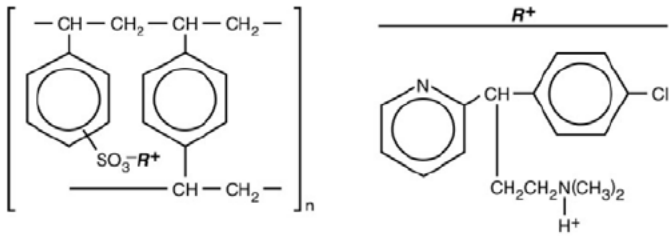
CAS#: [113-92-8]



Chlorpheniramine Polistirex

Molecular Formula: $C_{16}H_{19}ClN_2$ (chlorpheniramine)

Molecular Weight: 274.80 (chlorpheniramine)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	30-JUL-2010	Reviewed by G.Kang.
	II			3	Adequate	05-MAR-2010	Reviewed by X. Shen.
	II			4			
	IV			4			
	V			4			
	IV			4			(b) (4)
	IV			4			
	III			4			
	III			4			
	III			4			Meets the USP <660> test.
	IV			4			
	III			4			FDA 21 CFR 177.1210

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	acceptable	14-MAY-2010	A. Inyard
Methods Validation	N/A		
Labeling	acceptable	30-NOV-2009	B. Nour
Bioequivalence	Dissolution: acceptable BE studies: acceptable	28-MAY-2010 28-MAY-2010	T. Ramson S. Shrivastava
EA	Waiver submitted		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Expedited review

The Chemistry Review for ANDA 091632

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is **approvable**.

CMC section is acceptable.
Bio and labeling sections are acceptable.
EES is acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Tussionex Pennkinetic Extended-release Oral Suspension UCB Inc.

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension is for oral use only.
Hydrocodone release from Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension is controlled extended-release drug delivery system, which combines an ion-exchange polymer matrix with a diffusion rate-limiting permeable coating. Chlorpheniramine release is prolonged by use of an ion-exchange polymer system.

Inactive ingredients of the drug product are: Ascorbic acid, D&C Yellow No. 10, flavors, high fructose corn syrup, modified food starch, methylparaben, polysorbate 80, polyvinyl acetate, propylene glycol, propylparaben, purified water, sodium ascorbate, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, xanthan gum.

Drug product is manufactured by (b) (4) .

The processes and equipments used to manufacture the exhibit batch are functionally equivalent to the processes and equipments proposed to use in the scale-up batch.

The exhibit batches were packaged using 3 different proposed packaging systems placed on stability according their stability protocol. The firm submitted three months accelerated and room temperature stability data.
The firm has requested 24 months expiration date based on the three months accelerated stability data.

B. Description of How the Drug Product is Intended to be Used

Maximum Daily Dose is 2 x 5 mL as per Labeling insert information.

Hydrocodone bitartrate: 20 mg
Chlorpheniramine maleate: 16 mg

The drug substance: based on the ICH Guideline Q3A (R)
IT is 0.10% for any single unknown impurities (unspecified).
QT is 0.15% for any specified identified or specified unidentified impurity.

The drug product: based on the ICH Guideline Q3B (R)
IT is 0.2% for any single unknown impurities (unspecified).
QT is 0.5% for any specified identified or specified unidentified impurity.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry deficiencies are satisfactorily responded by telephone amendment.
Labeling and Bio sections are acceptable.
EES is acceptable.

25-MAY-2010 amendment:
Dissolution specification for release (3.2.P.5.1) and stability (3.2.P.8.2) has been revised in accordance with the FDA-recommended dissolution specification.

Following this page, 51 pages withheld in full (b)(4)

(b) (4)

[redacted]

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion:

A waiver is provide in Section 1.12.14.

III. List Of Deficiencies To Be Communicated

cc: ANDA 091632
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G. Kang, Ph.D./07-27-2010

HFD-630/S. H. Liu, Ph.D., Team Leader/08-09-2010

HFD-617/S. Nguyen, Pharm. D., PM/08-10-2010

F/T by : SN/08-10-2010

V:\Chemistry Division III\Team 4\ANDA REVIEWS\Gil\91632RV2_final.doc

TYPE OF LETTER: APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
08/10/2010

SHING HOU H LIU
08/10/2010
The CMC review is currently acceptable per the review team recommendations.
ANDA approvability is pending Division review, other disciplines and/or EES.
If changes or additions are deemed necessary at the Division level, an addendum will be written describing only those changes or additions

SARAH K NGUYEN
08/10/2010

ANDA 091632

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension

(Equivalent to 10 mg Hydrocodone Bitartrate and 8 mg Chlorpheniramine Maleate per 5 mL)

[Addendum to the review in DARRTS dated 10-AUG-2010]

Tris Pharma Inc.

Gil-Jong Kang
Office of Generic Drugs
Division of Chemistry III
Team 4

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 091632

2. REVIEW #: 2 (Addendum to the review in DARRTS dated 10-AUG-2010)

3. REVIEW DATE: 28-SEP-2010

4. REVIEWER: Gil-Jong Kang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Refuse to receive Amendment Date (received) acceptable for filing	13-JUL-2009 13-AUG-2009 26-AUG-2009 27-AUG-2009
Consult request (Sodium ascorbate) Expedited review granted Consult result (Sodium ascorbate)	28-AUG-2009 18-SEP-2009 01-OCT-2009
Deficiency letter based on review #1	25-FEB-2010
Minor amendment	16-MAR-2010
Amendment (Dissolution specification change)	25-MAY-2010
Telephone amendment Telephone amendment	01-JUL-2010 19-JUL-2010
Review #2	10-AUG-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone amendment	10-SEP-2010
Telephone amendment	14-SEP-2010
Telephone amendment	24-SEP-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Tris Pharma, Inc.

Address:	2033 Route 130 Monmouth Junction, NJ 08852
Representative:	W. Scott Groner
Telephone: Fax:	(732) 940-0358 (732) 940-0374

8. DRUG PRODUCT NAME:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension

9. LEGAL BASIS FOR SUBMISSION:
   Reference listed drug: Tussionex® Pennkinetic®
   Manufactured by UCB Inc.
   Application Number: N019111
   Strength: 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL
   Patent Certification: No unexpired patents for this product.
   Exclusivity: None

10. PHARMACOL. CATEGORY:
    Relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.

11. DOSAGE FORM:
    Extended-Release Oral Suspension

12. STRENGTH/POTENCY:
    10 mg Hydrocodone bitartrate and 8 mg Chlorpheniramine maleate per 5 mL

13. ROUTE OF ADMINISTRATION:
    Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

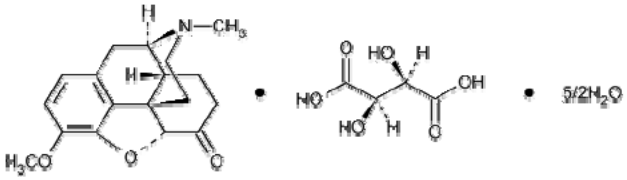
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    __X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

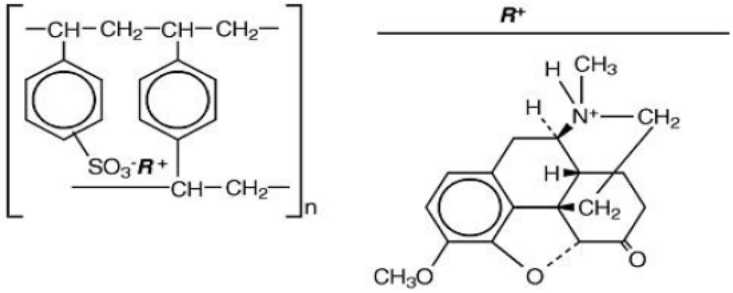
Hydrocodone Bitartrate:

4,5α -Epoxy-3-methoxy-17-methyl-morphinan-6-one tartrate (1:1) hydrate (2:5)
($C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 5/2\ H_2O$, MW = 494.50)
CAS#: 34195-34-1



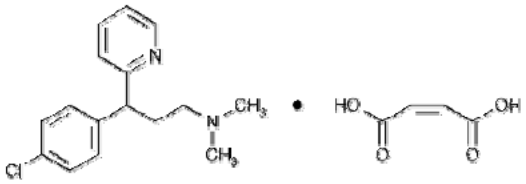
Hydrocodone Polistirex

Molecular Formula: $C_{18}H_{21}NO_3$ (hydrocodone)
Molecular Weight: 299.35 (hydrocodone)



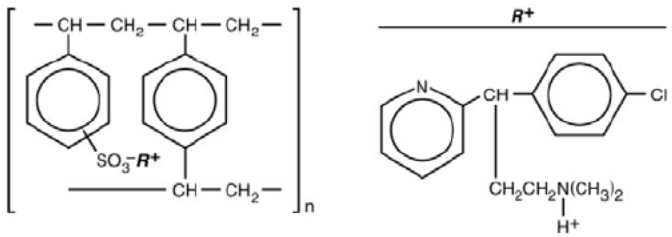
Chlorpheniramine Maleate:

2-[p-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1)
($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, MW = 390.86)
CAS#: [113-92-8]



Chlorpheniramine Polistirex

Molecular Formula: $C_{16}H_{19}ClN_2$ (chlorpheniramine)
Molecular Weight: 274.80 (chlorpheniramine)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	30-JUL-2010	Reviewed by G.Kang.
	II			3	Adequate	05-MAR-2010	Reviewed by X. Shen.
	II			4			
	IV			4			
	V			4			
	IV			4			(b) (4)
	IV			4			
	III			4			
	III			4			
	III			4			Meets the USP <660> test.
	IV			4			
	III			4			FDA 21 CFR 177.1210

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EES	acceptable	14-MAY-2010	A. Inyard
Methods Validation	N/A		
Labeling	acceptable	30-NOV-2009	B. Nour
Bioequivalence	Dissolution: acceptable BE studies: acceptable	28-MAY-2010 28-MAY-2010	T. Ramson S. Shrivastava
EA	Waiver submitted		
Radiopharmaceutical	N/A		
Pharm/Tox	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

Expedited review

The Chemistry Review for ANDA 091632

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

ANDA is **approvable**.

CMC section is acceptable.
Bio and labeling sections are acceptable.
EES is acceptable.

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A. Description of the Drug Product(s) and Drug Substance(s)

The reference listed drug for this application is Tussionex Pennkinetic Extended-release Oral Suspension UCB Inc.

Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally-acting narcotic antitussive. Chlorpheniramine is an antihistamine. Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension is for oral use only.
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Inactive ingredients of the drug product are: Ascorbic acid, D&C Yellow No. 10, flavors, high fructose corn syrup, modified food starch, methylparaben, polysorbate 80, polyvinyl acetate, propylene glycol, propylparaben, purified water, sodium ascorbate, sodium metabisulfite, sodium polystyrene sulfonate, sucrose, triacetin, xanthan gum.

Drug product is manufactured by (b) (4) .

The processes and equipments used to manufacture the exhibit batch are functionally equivalent to the processes and equipments proposed to use in the scale-up batch.

The exhibit batches were packaged using 3 different proposed packaging systems placed on stability according their stability protocol. The firm submitted three months accelerated and room temperature stability data.
The firm has requested 24 months expiration date based on the three months accelerated stability data.

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QT is 0.5% for any specified identified or specified unidentified impurity.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry deficiencies are satisfactorily responded by telephone amendments.
Labeling and Bio sections are acceptable.
EES is acceptable.

25-MAY-2010 amendment:
Dissolution specification for release (3.2.P.5.1) and stability (3.2.P.8.2) has been revised in accordance with the FDA-recommended dissolution specification.

24-SEP-2010 Telephone amendment:
Tris Pharma was called on 23-SEP-2010 and requested to provide scientific reasoning why they needed Sodium Metabisulfite (b) (4) in their formulation. **Use of Sodium Metabisulfite added a warning in the generic label not present in the RLD.**
In addition, Tris was requested to provide (b) (4)).

In the amendment dated 24-SEP-2010, Tris Pharma made a post approval commitment to manufacture (b) (4) .

Following this page, 56 pages withheld in full (b)(4)

(b) (4)

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

B. Environmental Assessment Or Claim Of Categorical Exclusion:

A waiver is provide in Section 1.12.14.

III. List Of Deficiencies To Be Communicated

cc: ANDA 091632
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G. Kang, Ph.D./07-27-2010

HFD-630/S. H. Liu, Ph.D., Team Leader/08-09-2010

HFD-617/S. Nguyen, Pharm. D., PM/08-10-2010

F/T by : SN/08-10-2010

V:\Chemistry Division III\Team 31\ANDA REVIEWS\Gil\91632RV2_final_addendum.doc

TYPE OF LETTER: APPROVABLE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
10/01/2010

SHING HOU H LIU
10/01/2010

STEVEN W YANG on behalf of ROBERT T GAINES
10/04/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	91632		
Drug Product Name	Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension		
Strength(s)	Eq. 8 mg and 10 mg/5 mL		
Applicant Name	Tris Pharma, Inc.		
Address	2033 Route 130, Monmouth Junction, NJ 08852		
Applicant's Point of Contact	W. Scott Groner, Dir. Reg. Affairs and Compliance		
Contact's Telephone Number	732-940-0358		
Contact's Fax Number	732-940-0374		
Original Submission Date(s)	**July 13, 2009**		
Submission Date(s) of Amendment(s) Under Review			
Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	S08-0404	S08-0405	
Study Type (s)	Fasting	Fed	
Strength (s)	Eq. 8 mg and 10 mg/5 mL		
Clinical Site	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301		
Clinical Site Address	See above		
Analytical Site	Cetero Research 10550 Rockley Road Suite 150 Houston, TX 77099		
Analytical Site Address	See above		
Dissolution Testing Site	Tris Pharma, Inc., 2033 Route 130, Monmouth Junction, NJ		
DSI Inspection Status	Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4) which has not been completed. Analytical Site Cetero Research, Houston, TX: Inspection completed on (b) (4) – Satisfactory.		
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**N/A**		
DSI REPORT RESULT	See above		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
Supporting Document # 1	**DISSOLUTION**	Eq. 8 mg CP and 10 mg HP/5 mL	**INADEQUATE**
Supporting Document # 1	**FASTING STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
ADEQUATE	**FED STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
	PERMEABILITY STUDY	**N/A**	**N/A**
	SOLUBILITY STUDY	**N/A**	**N/A**

1. EXECUTIVE SUMMARY

This application references Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (RLD Tussionex Pennkinetic®, NDA 19111, UCB Inc., Approved 12/31/1987), and includes one fasting and one fed bioequivalence (BE) study.

The fasting study is a single-dose, 2-treatment, 2-way crossover study in 29 normal healthy male and female volunteers given a dose of Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension Eq. to 8 mg and 10 mg/5 mL. The results (point estimate, 90% CI) for fasting study for hydrocodone and chlorpheniramine are as follows:

Fasting - Hydrocodone:

Parent Drug, Dose = Eq. 8 mg/10 mg Fasting Bioequivalence Study No. (S08-0404), (n=29) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	158.29	160.55	0.99	95.15	102.15
AUC∞ (ng·hr/mL)	160.89	162.85	0.99	95.43	102.29
Cmax (ng/mL)	14.56	15.05	0.97	93.12	100.48

Fasting - Chlorpheniramine:

Parent Drug, Dose = Eq. 8 mg/10 mg Fasting Bioequivalence Study No. (S08-0404), (n=29) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	391.48	408.30	0.96	91.37	100.62
AUC∞ (ng·hr/mL)	434.62	451.65	0.96	91.44	101.26
Cmax (ng/mL)	12.21	12.99	0.94	88.62	99.69

The fed study is a single-dose, 2-treatment, 2-way crossover study in 28 normal healthy male and female volunteers given a dose of Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension Eq. to 8 mg and 10 mg/5 mL. The results (point estimate, 90% CI) for fasting study for hydrocodone and chlorpheniramine are as follows:

Fed - Hydrocodone:

Parent Drug, Dose = Eq. 8 mg/10 mg Fed Bioequivalence Study No. (S08-0405), (n=28) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	185.07	188.93	0.98	93.72	102.38
AUC∞ (ng·hr/mL)	187.35	191.09	0.98	93.81	102.47
Cmax (ng/mL)	14.85	14.85	1.00	96.06	104.00

Fed - Chlorpheniramine:

Parent Drug, Dose = Eq. 8 mg/10 mg Fed Bioequivalence Study No. (S08-0405), (n=28) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	401.32	401.29	1.00	94.95	105.34
AUC∞ (ng·hr/mL)	437.44	439.71	0.99	93.66	105.67
Cmax (ng/mL)	11.55	11.62	0.99	93.41	105.88

The fasting and fed studies are **acceptable**.

A "dissolution only" review was not conducted on this ANDA. There is no USP method for this product, but there is an FDA-recommended method [495 mL SGF using Paddle at 50 rpm] See Dissolution method and specifications (NDA)

The firm conducted dissolution testing with a non-FDA-recommended method [(495 mL 0.1 N HCl for 1 hour, followed by 895 mL phosphate buffer (obtained by adding 400 mL of 0.27M disodium phosphate), Paddle at 50 rpm]. The firm has also conducted multimedia dissolution testing. The firm has conducted all the dissolution testing for 12 hours only (probably because drug is administered every 12 hours – see Tussionex® labeling), therefore, the % dissolution never reached 80%. The innovator on the other hand conducted dissolution testing for 24 hours and has shown that % dissolution reaches 80% and has 24 hour time point in the specification. The firm should conduct additional dissolution testing. The dissolution testing is **incomplete**.

The firm has submitted the CTD summary tables.

Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4), which has not been completed.

Analytical Site Cetero Research, Houston, TX: Inspection completed on (b) (4) – Satisfactory.

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1.Drug Product Information

Test Product	Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-Release **suspension**, 8 mg/10 mg (equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate) per 5 mL suspension
Reference Product	Tussionex® Pennkinetic® (chlorpheniramine polistirex and hydrocodone polistirex) Extended-Release **Oral Suspension**, equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate per 5 mL suspension
RLD Manufacturer	UCB Inc.
NDA/ANDA No.	19-111
RLD Approval Date	December 31, 1987
Indication	Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.

3.2.PK/PD Information[1]

Bioavailability	Both are well absorbed, but no data is available on the bioavailability.
Food Effect	Chlorpheniramine: Delays absorption but does not alter BA Hydrocodone: No effect of food reported; alcohol should be avoided
Tmax	Chlorpheniramine: ~6.3 hrs. Hydrocodone: 3.4 hrs.
Metabolism	Chlorpheniramine: Extensive first-pass metabolism; Metabolites: 1) Didesmethyl Derivatives (inactive), 2) Monodesmethyl Derivatives (inactive) Hydrocodone: Metabolized by CYP 2D6 in the liver. Approximately 7% of Caucasians, 3% of blacks, and 1 % of Asians are poor metabolizers and will experience little or no analgesia from hydrocodone. Six (known) metabolites produced: ** 1) Hydromorphone (active) 2) Norcodeine (active) 3) 6-beta-hydrocodol (active) 4) 6-alpha-hydrocodol (active) 5) 6-beta-hydromorphol (active).
Excretion	Chlorpheniramine: Renal – 50%, Fecal – <1% Hydrocodone: Renal: 26% (approximately 70% o f total excretion of hydrocodone and metabolites occur in the first 24 hours; hydrocodone, norcodeine, and hydromorphone have been detectable at 72 hours after a single oral dose).
Half-life	Chlorpheniramine: 20 hrs. Hydrocodone: 3.8-4.5 hrs.
Agency Guidance	None
Drug Specific Issues	None

**Each of the above listed metabolites has pharmacological activity ≥ parent

[1] http://csi micromedix.com/

Relevant OGD or DBE History	**ANDA:** 77-273 (Tyco Health Care, for capsule), [redacted], 91-671 (Cornerstone Therapeutics). **CD:** 04-009 (Cornerstone), 06-0677 [redacted], 07-0692 [redacted], 07-1036 [redacted], 08-0069 [redacted] The DBE recommended the following: a. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing your Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension to the reference listed drug (RLD), Tussionex (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Extended-Release Oral Suspension. b. A single-dose, two-way crossover fed in-vivo bioequivalence study comparing your Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension to the RLD. c. Please measure both hydrocodone and chlorpheniramine. d. Please develop a dissolution method for this product and conduct comparative dissolution testing on 12 dosage units of the test and reference products. A dosage unit for a suspension is the labeled strength (5 ml). A total of 12 units from 12 different bottles should be used. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus I1 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. **Protocol: P06-003 (SFBC)**
Drug Specific Issues	

NOT FOR RELEASE UNDER F.O.I.

Dissolution method and specifications (NDA)[3]

Medium:	Simulated Gastric Fluid (SGF) at 37ºC ± 0.5ºC
Volume:	495 mL
Apparatus:	USP apparatus II (Paddle)
Speed:	50 rpm
FDA-Recommended Specifications:	
• Hydrocodone	1 hour: [redacted] 3 hours: 8 hours: 24 hour
• Chlorpheniramine	1 hour: [redacted] 3 hours: 8 hours: 24 hour

[2] Control Document Database, CD 08-0069 [redacted] \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0069.pdf
[3] OCPB Review of NDA 19-111, CHOI, YOUNG M 02/01/2002 N/A 02/01/2002 Archive, http://darrts fda.gov:7777/darrts/ViewDocument?documentId=090140af8013dbf7

3.3.OGD Recommendations for Drug Product[4]

Number of studies recommended:	2, Fasting and Fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 8 mg and 10 mg/5 mL
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	Eq. 8 mg and 10 mg/5 mL
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

Analytes to measure (in plasma/serum/blood):	Chlorpheniramine Maleate and hydrocodone
Bioequivalence based on:	(90% CI)
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Control Document Database, CD 08-0069 (b) (4) \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0069.pdf

[4] Control Document Database, CD 08-0069 (b) (4) \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0069.pdf

	ANDA: 77-273 (Tyco Health Care, for capsule), (b) (4) (b) (4), 91-671 (Cornerstone Therapeutics). **CD:** 04-009 (Cornerstone), 06-0677 (b) (4) 07-0692 (b) (4) 07-1036 (b) (4) 08-0069 (b) (4). The DBE recommended the following: a. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing your Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension to the reference listed drug (RLD), Tussionex (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Extended-Release Oral Suspension. b. A single-dose, two-way crossover fed in-vivo bioequivalence study comparing your Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension to the RLD. c. Please measure both hydrocodone and chlorpheniramine. d. Please develop a dissolution method for this product and conduct comparative dissolution testing on 12 dosage units of the test and reference products. A dosage unit for a suspension is the labeled strength (5 ml). A total of 12 units from 12 different bottles should be used. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus I1 at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. **Protocol: P06-003 (SFBC)** – Same BE recommendations as above.

3.4.Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

[5] Control Document Database, CD 08-0069 (b) (4) \\cdsnas\OGDS6\CONTROLS\2008-docs\08-0069.pdf

3.5.Pre-Study Bioanalytical Method Validation

Bioanalytical Method Validation - Hydrocodone

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4
Analyte	Hydrocodone
Internal standard (IS)	(b) (4)
Method description	Liquid-liquid extraction with LC/MS/MS method
Limit of quantitation (ng/mL)	0.1000 ng/mL
Average recovery of drug (%)	63.7%
Average recovery of IS (%)	65.9%
Standard curve concentrations (ng/mL)	0.1000, 0.2000, 0.4000, 0.5000, 1.000, 2.000, 5.000, 20.00, 40.00 and 50.00 ng/mL
QC concentrations (ng/mL)	0.2500, 3.000 and 37.50 ng/mL
QC Intraday precision range (%)	0.5 to 4.6% (LQC, MQC, HQC and ULOQ) 6.4 to 11.2% (LLOQ)
QC Intraday accuracy range (%)	-3.9 to 8.7% (LQC, MQC, HQC and ULOQ -0.4 to 0.6% (LLOQ)
QC Interday precision range (%)	2.3 to 3.3% (LQC, MQC, HQC and ULOQ) 8.8% (LLOQ)
QC Interday accuracy range (%)	-2.9 to 7.0% (LQC, MQC, HQC and ULOQ) 0.1% (LLOQ)
Bench-top stability (hrs)	24 hours in human plasma @ room temperature
Stock stability (days/hours)	6 hours @ room temperature for drug and internal standard 13 hours @ 4°C for drug and internal standard
Processed stability (hrs)	59 hours @ room temperature; 59 hours @ 4°C
Freeze-thaw stability (cycles)	6 freeze-thaw cycles
Long-term storage stability (days)	206 days @ -20°C
Dilution integrity	250.0 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

Refer to the bioanalytical method validation report for the method validation SOPs.

Bioanalytical Method Validation - Chlorpheniramine

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4
Analyte	Chlorpheniramine maleate
Internal standard (IS)	(b) (4)
Method description	Liquid-liquid extraction with LC/MS/MS method
Limit of quantitation (pg/mL)	0.2000 ng/mL
Average recovery of drug (%)	79.4%
Average recovery of IS (%)	65.9%
Standard curve concentrations (pg/mL)	0.2000, 0.4000, 0.8000, 1.000, 2.000, 4.000, 10.00, 40.00, 80.00 and 100.0 ng/mL
QC concentrations (pg/mL)	0.5000, 6.000 and 75.00 ng/mL
QC Intraday precision range (%)	0.9 to 4.3% (LQC, MQC, HQC and ULOQ) 6.5 to 7.3% (LLOQ)
QC Intraday accuracy range (%)	-6.7 to 4.8% (LQC, MQC, HQC and ULOQ) 0.8 to 4.2% (LLOQ)
QC Interday precision range (%)	2.4 to 5.2% (LQC, MQC, HQC and ULOQ) 6.7% (LLOQ)
QC Interday accuracy range (%)	-3.2 to 2.9% (LQC, MQC, HQC and ULOQ) 2.5% (LLOQ)
Bench-top stability (hrs)	24 hours in human plasma @ room temperature
Stock stability (days)	6 hours @ room temperature for drug and internal standard 13 hours @ 4°C for drug and internal standard
Processed stability (hrs)	59 hours @ room temperature; 59 hours @ 4°C
Freeze-thaw stability (cycles)	6 freeze-thaw cycles
Long-term storage stability (days)	206 days @ -20°C
Dilution integrity	500.0 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

Refer to the bioanalytical method validation report for the method validation SOPs.

Comments on the Pre-Study Method Validation: Acceptable. K2-EDTA anticoagulant was used for methods validations as well as for the subject samples.

3.6.In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Fasted Bioequivalence Study – Hydrocodone

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-inf} (ng-hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	
CRI-00014527/ **S08-0404**/ R09-0218	A Relative Bioavailability Study of Hydrocodone Polistirex ER (eq. to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (eq. to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fasted Conditions	Randomized, single-dose, two-way, open-label crossover study	Test: Hydrocodone Polistirex / Chlorpheniramine Polistirex ER Oral Suspension, 5 mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL) [Lot No. TB-047A]	30 (19/11) Healthy volunteers 34.2 yr (18 – 58 yr)	14.96 (24.68)	2.75 (1.50-5.00)	163.73 (27.00)	167.10 (26.89)	10.93 (61.82)	0.0786 (35.69)	5.3.1.2
			Reference: Tussionex® Pennkinetic® ER Oral Suspension, 5mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL); [Lot No. 41648]		15.48 (24.10)	3.00 (1.00-4.50)	166.39 (26.06)	169.50 (26.18)	11.21 (56.76)	0.0767 (37.59)	

[1]Subjects used in final statistical report

Fasted Bioequivalence Study – Chlorpheniramine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-inf} (ng-hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	
CRI-00014527/ **S08-0404**/ R09-0218	A Relative Bioavailability Study of Hydrocodone Polistirex ER (eq. to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (eq. to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fasted Conditions	Randomized, single-dose, two-way, open-label crossover study	Test: Hydrocodone Polistirex / Chlorpheniramine Polistirex ER Oral Suspension, 5 mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL) [Lot No. TB-047A] Reference: Tussionex® Pennkinetic® ER Oral Suspension, 5mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL); [Lot No. 41648]	29 (18/11) Healthy volunteers 34.1 yr (18 – 58 yr)	12.70 (30.43)	6.50 (4.00 - 14.00)	426.16 (41.97)	477.32 (47.68)	25.82 (30.58)	0.0294 (31.74)	5.3.1.2
					13.34 (24.32)	6.50 (4.50 - 12.00)	436.42 (36.79)	492.79 (43.79)	26.62 (30.27)	0.0284 (31.58)	

[1]Subjects used in final statistical report

Fed Bioequivalence Study – Hydrocodone

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-inf} (ng-hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	
CRI-00014528/ **S08-0405**/ R09-0219	A Relative Bioavailability Study of Hydrocodone Polistirex ER (eq. to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (eq. to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fed Conditions	Randomized, single-dose, two-way, open-label crossover study	Test: Hydrocodone Polistirex / Chlorpheniramine Polistirex ER Oral Suspension, 5 mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL) [Lot No. TB-047A] Reference: Tussionex® Pennkinetic® ER Oral Suspension, 5mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL); [Lot No. 41648]	28 (17/11) Healthy volunteers 31.8 yr (18 – 57 yr)	15.22 (23.05)	4.50 (2.50-6.00)	193.08 (31.19)	196.13 (31.16)	9.74 (49.40)	0.0839 (34.99)	5.3.1.2
					15.09 (18.62)	3.76 (2.50-5.00)	195.41 (27.84)	198.32 (27.88)	10.78 (48.56)	0.0755 (35.89)	

[1]Subjects used in final statistical report

Fed Bioequivalence Study – Chlorpheniramine

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects[1] No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters[1] Median (Range) for T_{max}						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng-hr/mL)	AUC_{0-inf} (ng-hr/mL)	$T_{1/2}$ (hr)	Kel (1/hr)	
CRI-00014528/ **S08-0405**/ R09-0219	A Relative Bioavailability Study of Hydrocodone Polistirex ER (eq. to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (eq. to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fed Conditions	Randomized, single-dose, two-way, open-label crossover study	Test: Hydrocodone Polistirex / Chlorpheniramine Polistirex ER Oral Suspension, 5 mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL) [Lot No. TB-047A] Reference: Tussionex® Pennkinetic® ER Oral Suspension, 5mL (eq. to 10 mg hydrocodone bitartrate / 8 mg Chlorpheniramine maleate per 5 mL); [Lot No. 41648]	28 (17/11) Healthy volunteers 31.8 yr (18 – 57 yr)	12.17 (34.59)	7.50 (4.50 - 16.00)	447.04 (50.22)	497.22 (56.95)	23.18 (34.37)	0.0330 (29.94)	5.3.1.2
					12.02 (28.69)	9.01 (6.00 - 16.00)	441.12 (47.62)	482.28 (55.40)	22.02 (34.82)	0.0347 (29.65)	

[1]Subjects used in final statistical report

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Firm (n = 29)

Statistical Summary of the Comparative Bioavailability Data – Hydrocodone

Hydrocodone 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=30[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	158.11	160.46	98.54	(95.00, 102.20)
AUC_{0-inf}	161.38	163.45	98.73	(95.36, 102.23)
C_{max}	14.56	15.05	96.73	(93.12, 100.48)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	184.85	188.84	97.89	(93.61, 102.36)
AUC_{0-inf}	187.76	191.65	97.97	(93.74, 102.40)
C_{max}	14.85	14.85	99.95	(96.06, 104.00)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Statistical Summary of the Comparative Bioavailability Data – Chlorpheniramine

Chlorpheniramine 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=29[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	391.89	409.19	95.77	(91.25, 100.52)
AUC_{0-inf}	431.33	452.78	95.26	(90.41, 100.37)
C_{max}	12.21	12.99	93.99	(88.62, 99.69)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	401.31	399.80	100.38	(95.24, 105.79)
AUC_{0-inf}	435.25	430.18	101.18	(96.25, 106.35)
C_{max}	11.55	11.62	99.45	(93.41, 105.88)

[1]Geometric means are based on least squares means of ln-transformed values
[2]Subjects used in final statistical report

Table 3. Statistical Summary of the BE Data Calculated by the Reviewer – Fasting: Hydrocodone (n=29)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	158.29	160.55	0.99	95.15	102.15
LAUCI	160.89	162.85	0.99	95.43	102.29
LCMAX	14.56	15.05	0.97	93.12	100.48

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 4. Statistical Summary of the BE Data Calculated by the Reviewer – Fasting: Chlorpheniramine (n=29)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	391.48	408.30	0.96	91.37	100.62
LAUCI	434.62	451.65	0.96	91.44	101.26
LCMAX	12.21	12.99	0.94	88.62	99.69

Table 5. Statistical Summary of the BE Data Calculated by the Reviewer – Fed: Hydrocodone (n=28)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	185.07	188.93	0.98	93.72	102.38
LAUCI	187.35	191.09	0.98	93.81	102.47
LCMAX	14.85	14.85	1.00	96.06	104.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 6. Statistical Summary of the BE Data Calculated by the Reviewer – Fed: Chlorpheniramine (n=28)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	401.32	401.29	1.00	94.95	105.34
LAUCI	437.44	439.71	0.99	93.66	105.67
LCMAX	11.55	11.62	0.99	93.41	105.88

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Comment: The statistical analysis was done with CALCKE.SAS program using plasma concentration dataset. The reviewer checked every subject for Cmax, AUCt and AUCi. The firm has appropriately calculated Ke for all subjects. There were no PK repeats. The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted the repeat values or the average of all determinations, which is appropriate and according to the SOP.

Table 7. Reanalysis of Study Samples - Fasted Study Hydrocodone

Study No. S08-0404 Hydrocodone Additional information in Volume(s) I, Page(s) 14 to 15 and 30								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low internal standard	1	5	0.06	0.28	1	5	0.06	0.28
Data acquisition malfunction (incident cannot be attributable to any specific individual component of the laboratory acquisition system)	1	1	0.06	0.06	1	1	0.06	0.06
Laboratory accident (sample spillage and/or tube broken during sample extraction)	1	0	0.06	0.00	1	0	0.06	0.00
High internal standard	0	1	0.00	0.06	0	1	0.00	0.06
Total	3	7	0.17	0.39	3	7	0.17	0.39

[1] If no repeats were performed for pharmacokinetic reasons, insert “0.0” throughout the table

Table 8. Reanalysis of Study Samples- Fasted Study Chlorpheniramine

Study No. S08-0404 Chlorpheniramine Additional information in Volume(s) I, Page(s) 15 and 31								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low internal standard	1	5	0.06	0.28	1	5	0.06	0.28
Data acquisition malfunction (incident cannot be attributable to any specific individual component of the laboratory acquisition system)	1	1	0.06	0.06	1	1	0.06	0.06
Laboratory accident (sample spillage and/or tube broken during sample extraction)	1	0	0.06	0.00	1	0	0.06	0.00
Retention time shift	1	0	0.06	0.00	1	0	0.06	0.00
High internal standard	0	1	0.00	0.06	0	1	0.00	0.06
Peak in pre-dose sample	1	0	0.06	0.00	1	0	0.06	0.00
Total	5	7	0.28	0.39	5	7	0.280	0.39

[1] If no repeats were performed for pharmacokinetic reasons, insert “0.0” throughout the table

Table 9. Reanalysis of Study Samples - Fed Study Hydrocodone

Study No. S08-0405 Hydrocodone Additional information in Volume(s) I, Page(s) 15 and 33								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Extraction problem (emulsion occurred and sample was very cloudy after extraction)	0	1	0.00	0.06	0	1	0.00	0.06
Low internal standard	1	0	0.06	0.00	1	0	0.06	0.00
Peak in pre-dose sample	0	1	0.00	0.06	0	1	0.00	0.06
High internal standard	0	1	0.00	0.06	0	1	0.00	0.06
Total	1	3	0.06	0.18	1	3	0.06	0.18

[1] If no repeats were performed for pharmacokinetic reasons, insert “0.0” throughout the table

Table 10. Reanalysis of Study Samples - Fed Study Chlorpheniramine

Study No. S08-0405 Chlorpheniramine Additional information in Volume(s) I, Page(s) 15 and 34								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Low internal standard	2	0	0.12	0.00	2	0	0.12	0.00
Extraction problem (emulsion occurred and sample was very cloudy after extraction)	0	1	0.00	0.06	0	1	0.00	0.06
Peak in pre-dose sample	1	0	0.06	0.00	1	0	0.06	0.00
Total	3	1	0.18	0.06	3	1	0.18	0.06

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout the table

Did use of recalculated plasma concentration data change study outcome? The firm properly identified every sample mentioned in above table. The reviewer agrees with the firm's assessment. The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted the repeat values or the average of all determinations, which is appropriate and according to the SOP. There were no PK repeats.

Comments from the Reviewer: Reanalysis is acceptable.

3.7. Formulation

Location in appendix	See Formulation Data
If a tablet, is the RLD scored?	Not applicable
If a tablet, is the test product biobatch scored	Not applicable
Is the formulation acceptable?	**ACCEPTABLE**
If not acceptable, why?	N/A

3.8. Dissolution Method

Source of Method	Firm
Medium	Acidic medium at 0.1 N HCl for 1 hour followed by phosphate buffer until 12 hrs.
Volume (mL)	495 and 895 mL
USP Apparatus type	I1 (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	1 Hr. - (b) (4) 3 Hrs. 6 Hrs. 12 Hrs
FDA-recommended specifications[6]	FDA-recommended method and specifications differ, see Dissolution method and specifications (NDA)
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	Incomplete
If not then why?	The firm has used its own method. It should conduct dissolution testing using the FDA-recommended method.

3.9.Waiver Request(s)

Strengths for which waivers are requested	N/A. Only one strength
Is dissolution acceptable?	No
Waivers granted?	N/A
If not then why?	N/A

3.10. Deficiency Comments

1. The firm has proposed the following method:

   Apparatus: 2 (Paddle) at 50 rpm
   Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27 M Disodium Phosphate to obtain buffer solution (pH not mentioned)
   Temperature: 37 ±0.5°C
   Sampling Time: 1, 3, 6 and 12 hours

   The firm should provide the pH of the medium after adding 400 mL of 0.27 M disodium phosphate to the 495 mL of 0.1 N HCl and continue the dissolution testing for 24 hours or until 80% of each of the drug in the dosage forms is dissolved.

[6] Dissolution Database (Internal), (b) (4)

2. The firm should also conduct dissolution testing with the FDA-recommended method as follows and submit data for the test and reference products for evaluation:

   Medium: 495 mL Simulated Gastric Fluid (SGF) at 37ºC
   Apparatus: USP 2 (Paddle) at 50 rpm
   Sampling Time: 1, 3, 8, 24 hours or until 80% of the each drug in the dosage form is dissolved

3. The firm has conducted dissolution testing in other media, viz., buffers at pH 1.2, 4.5 and 6.8. However, the firm has not provided the summarized dissolution data (testing date, mean dissolution, range, %CV, etc. for the test and reference products) in tables. The firm should provide the summary data. The dissolution data on the individual dosage units are not legible. The firm should provide a legible copy of these dissolution testing results.

a. Recommendations

1. The Division of Bioequivalence finds the fasting BE study (#S08-0404) is **acceptable**. Tris Pharma, Inc. conducted the fasting BE study on its Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) comparing it to UCB's Tussionex Pennkinetic®, Eq. 8 mg and 10 mg/5 mL (Lot #41648).

2. The Division of Bioequivalence finds the fed BE study (#S08-0405) is **acceptable**. Tris Pharma, Inc. conducted the fasting BE study on its Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) comparing it to UCB's Tussionex Pennkinetic®, Eq. 8 mg and 10 mg/5 mL (Lot #41648).

3. The firm conducted dissolution testing with a non-FDA-recommended method. The dissolution testing conducted by Tris Pharma, Inc. on its Chlorpheniramine Polistirex and Hydrocodone Polistirex Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) is **incomplete** due to deficiencies #1-3 cited above.

b. Comments for Other OGD Disciplines

Discipline	Comment
None	

4. APPENDIX

a. Individual Study Reviews

i. Single-dose Fasting Bioequivalence Study

1. Study Design

Table 11 Study Information - Fasting Study

Study Number	CRI-00014527/**S08-0404**/R09-0218
Study Title	A Relative Bioavailability Study of Hydrocodone Polistirex ER (Equivalent to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (Equivalent to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fasted Conditions
Clinical Site (Name, Address, Phone #)	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301, USA (636)757-7074
Principal Investigator	Ramón Vargas, M.D., M.P.H.
Dosing Dates	Period I: 26 April 2009
	Period II: 10 May 2009
Analytical Site (Name, Address, Phone #)	Cetero Research, 10550 Rockley Road, Suite 150, Houston, TX 77099, 281-495-6996
Analysis Dates	May 20, 2009 to May 27, 2009
Analytical Director	(b) (6) M.S.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	April 26, 2009 to May 27, 2009 (31 days)

Table 12. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension	Tussionex® Pennkinetic®
Manufacturer	Manufactured by Tris Pharma, Inc.	Manufactured by Celltech Manufacturing, Inc.
Batch/Lot No.	TB-047A	41648
Manufacture Date	04/01/09	N/A
Expiration Date	N/A	05/2009
Strength	hydrocodone polistirex (equivalent to 10 mg hydrocodone bitartrate) and chlorpheniramine polistirex (equivalent to 8 mg chlorpheniramine maleate) per 5 mL	hydrocodone polistirex (equivalent to 10 mg hydrocodone bitartrate) and chlorpheniramine polistirex (equivalent to 8 mg chlorpheniramine maleate) per 5 mL
Dosage Form	ER Oral Suspension	ER Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency – Hydrocodone	95.6%, 95.6%	97.7%, 96.5%
Potency - Chlorpheniramine	101.9%, 101.9%	100.0%, 100.0%
Content Uniformity (mean, %CV)	N/A	N/A
Dose Administered	1 × 5 mL (hydrocodone polistirex [equivalent to 10 mg hydrocodone bitartrate] and chlorpheniramine polistirex [equivalent to 8 mg chlorpheniramine maleate])	1 × 5 mL (hydrocodone polistirex [equivalent to 10 mg hydrocodone bitartrate] and chlorpheniramine polistirex [equivalent to 8 mg chlorpheniramine maleate])
Route of Administration	Oral	Oral

Table 13. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	30 Subjects were dosed; 30 completed the study; 30 subject samples were analyzed.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 1, 3, 4, 8, 10, 12, 13, 16, 18, 21, 23, 24, 26, 27, 29 BA: 2, 5, 6, 7, 9, 11, 14, 15, 17, 19, 20, 22, 25, 28, 30
Blood Sampling Times	Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 24, 36, 48, 72 and 96 hrs. post-dose
Blood Volume Collected/Sample	6 mL in K2EDTA Vacutainers. K3EDTA was never used.
Blood Sample Processing/Storage	After collection, blood samples were cooled; immediately centrifuged; plasma samples were separated, and stored at -20 ^{0}C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects fasted overnight for at least 10 hours prior to drug administration and then for a further 4 hours following drug administration.
Length of Confinement	Subjects were confined to clinical facility from at least 10 hours prior to each drug administration until after the 24-hour blood sample collection.
Safety Monitoring	Subjects were monitored throughout the study.
Drug Specific Information	None

Comments on Study Design: The study design is acceptable.

2. Clinical Results

Table 14. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasted Bioequivalence Study - Hydrocodone

CRI-00014527/S08-0404/R09-0218			
		Treatment Groups	
		Test Product N=30[1]	Reference Product N=30[1]
Age (years)	Mean ± SD	34.2 ± 12.7	34.2 ± 12.7
	Range	18 - 58	18 - 58
Age Groups	< 18	-	-
	18 – 39	21 (70.0%)	21 (70.0%)
	40 – 64	9 (30.0%)	9 (30.0%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	19 (63.3%)	19 (63.3%)
	Female	11 (36.7%)	11 (36.7%)
Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	-	-
Not Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	3 (10.0%)	3 (10.0%)
	I	-	-
	W	27 (90.0%)	27 (90.0%)
BMI	Mean ± SD	26.0 ± 3.3	26.0 ± 3.3
	Range	20 - 32.1	20 - 32.1
Other Factors			

[1] Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Fasted Bioequivalence Study – Chlorpheniramine

CRI-00014527/S08-0404/R09-0218			
		Treatment Groups	
		Test Product N=29[1]	Reference Product N=29[1]
Age (years)	Mean ± SD	34.1 ± 12.9	34.1 ± 12.9
	Range	18 - 58	18 - 58
Age Groups	< 18	-	-
	18 – 39	20 (69.0%)	20 (69.0%)
	40 – 64	9 (31.0%)	9 (31.0%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	18 (62.1%)	18 (62.1%)
	Female	11 (37.9%)	11 (37.9%)
Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	-	-
Not Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	3 (10.3%)	3 (10.3%)
	I	-	-
	W	26 (89.7%)	26 (89.7%)
BMI	Mean ± SD	26.0 ± 3.3	26.0 ± 3.3
	Range	20 - 32.1	20 - 32.1
Other Factors			

[1] Subjects used in final statistical report

Table 15. Dropout Information, Fasting Bioequivalence Study

CRI-00014527 (Cetero Research – St. Charles S08-0404)				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
N/A	N/A	N/A	N/A	N/A

Table 16. Incidence of Adverse Events in Individual Studies - Fasted Study

Body System/Adverse Event[1]	**Reported Incidence by Treatment Groups**	
	CRI-00014527/S08-0404/R09-0218	
	Test N=30[2]	**Reference N=30**[2]
	n (%)[3]	**n (%)**[3]
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (6.67%)	-
Pain in extremity	1 (3.33%)	-
Nervous system disorders		
Dizziness	-	1 (3.33%)
Headache	3 (10.00%)	2 (6.67%)
Hypoaesthesia	1 (3.33%)	-
Respiratory, thoracic and mediastinal disorders		
Sinus headache	1 (3.33%)	-
Total	6 (20.00%)	3 (10.00%)

[1] MedDRA Version 11.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 17. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject No. (Test)	Subject No. (Reference)
Subject was approved for dosing Period I with out of range vital signs by Ramón Vargas, M.D., M.P.H., the Principal Investigator	003, 024	
Subject was approved for dosing Period II with out of range vital signs by Ramón Vargas, M.D., M.P.H., the Principal Investigator	011	008
Period I, Hour 48 respirations not obtained due to staff error	024	
Period I vital signs obtained outside of the ±30 minute window due to schedule conflict	008, 024	019
Period I vital signs not obtained due to failure to return to clinic	008, 012, 013	
Period II vital signs obtained outside of the ±30 minute window due to schedule conflict	005	008
Period II vital signs not obtained due to failure to return to clinic		024
Period I adverse event query not obtained due to failure to return to clinic	008, 012, 013	
Period II adverse event query not obtained due to failure to return to clinic		024

Pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times. These deviations did not have an impact on the results.

Comments on Dropouts/Adverse Events/Protocol Deviations: The dropouts were appropriate. Adverse events and deviations were minor and did not compromise the outcome of the study.

3. Bioanalytical Results

Table 18. Assay Validation – Within the Fasting BE Study - Hydrocodone

Bioequivalence Study No. S08-0404 Hydrocodone										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.10	0.20	0.40	0.50	1.00	2.00	5.00	20.0	40.0	50.0
Inter day Precision (%CV)	1.7	3.4	2.3	2.7	2.3	2.3	3.1	1.2	3.5	2.5
Inter day Accuracy (%Bias)	3.5	-3.8	-4.5	-2.8	0.5	-0.9	1.9	2.4	0.7	3.0
Linearity	0. 993508 to 0. 999227									
Linearity Range (ng/mL)	0.1000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.1000									

Bioequivalence Study No. S08-0404 Hydrocodone			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.2500	3.000	37.50
Inter day Precision (%CV)	6.2	2.8	3.9
Inter day Accuracy (%Bias)	4.8	-1.6	0.3

Table 19. Assay Validation – Within the Fasting BE Study - Chlorpheniramine

Bioequivalence Study No. S08-0404 Chlorpheniramine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.20	0.40	0.80	1.00	2.00	4.00	10.0	40.0	80.0	100
Inter day Precision (%CV)	1.3	2.2	2.9	4.0	2.6	2.6	2.9	1.7	3.1	2.1
Inter day Accuracy (%Bias)	4.8	-5.7	-5.9	-3.3	-0.2	-1.2	2.6	3.0	1.7	3.8
Linearity	0. 993318 to 0. 998815									
Linearity Range (ng/mL)	0.2000 to 100.0									
Sensitivity/LOQ (ng/mL)	0.2000									

Bioequivalence Study No. S08-0404 Chlorpheniramine			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.5000	6.000	75.00
Inter day Precision (%CV)	4.5	3.5	3.7
Inter day Accuracy (%Bias)	4.3	-1.3	1.8

Comments on Study Assay Validation: The calibration curve standards and QC samples were prepared in blank plasma fortified with K2EDTA anticoagulant. The assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial

Comments on Chromatograms: Acceptable

Table 20. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CET_SOP_04_LBP_006, Version 1	03/18/09	Sample Reanalysis and Reporting Criteria

Table 21. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	There were no PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Repeat Analysis: Fasting - Hydrocodone

Table 9 Summary of Repeat Analysis Data for Hydrocodone in Human Plasma

Subject	Period	Time	Custom ID	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for ReportedConc.
0004	1	6h	(b) (4)	(b) (4)	4	1	(b) (4)	33	(b) (4)	1
0008	2	96h			8	2		33		2
0009	1	6.5h			9	3		33		2
0012	2	16h			12	3		33		2
0017	1	96h			17	4		33		3
0017	2	96h			17	4		33		3
0022	1	1.5h			22	3		33		2
0022	1	3.5h			22	3		33		2
0023	1	6h			23	3		33		2
0024	2	7.5h			24	3		33		2

REASONS FOR REASSAY:
1). LA - Laboratory accident (sample spillage and/or tube broken during sample extraction)
2). HIS - High internal standard
3). LIS - Low internal standard
4). DAM - Data acquisition malfunction (incident cannot be attributable to any specific individual component of the laboratory acquisition system)

REASONS FOR REPORTED CONC:
1). Good extraction
2). Good extraction & Mean of original and repeat values used, original and repeat values are within 30%
3). Good injection

Repeat Analysis: Fasting - Chlorpheniramine

Table 10 Summary of Repeat Analysis Data for Chlorpheniramine in Human Plasma

Subject	Period	Time	Custom ID	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for Reported Conc.
0004	1	6h	(b) (4)	(b) (4)	4	1	(b) (4)	33	(b) (4)	1
0008	1	24h			8	2		33		2
0008	2	96h			8	3		33		3
0009	1	6.5h			9	4		33		3
0012	2	16h			12	4		33		3
0014	2	0h			14	5		33, 33, 33		4
0017	1	96h			17	6		33		2
0017	2	96h			17	6		33		2
0022	1	1.5h			22	4		33		3
0022	1	3.5h			22	4		33		3
0023	1	6h			23	4		33		3
0024	2	7.5h			24	4		33		3

REASONS FOR REASSAY:
1). LA - Laboratory accident (sample spillage and/or tube broken during sample extraction)
2). RTS - Retention time shift
3). HIS - High internal standard
4). LIS - Low internal standard
5). PIPD - Peak in pre-dose sample
6). DAM - Data acquisition malfunction (incident cannot be attributable to any specific individual component of the laboratory acquisition system)

REASONS FOR REPORTED CONC:
1). Sample successfully analyzed
2). Good injection
3). Good extraction & Mean of original and repeat values used, original and repeat values are within 30%
4). Mean of original and repeat values used, mean within 30% difference

Summary/Conclusions, Study Assays: The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted repeat values or the average of all

determinations, which is appropriate and according to the SOP. Sample re-analyses are acceptable.

4. Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis: Study #S08-0404

- The reviewer calculated the 90% confidence intervals for 29 and 30 subjects, respectively, for hydrocodone and chlorpheniramine maleate. Subject #14 had >5% of Cmax value for Chlorpheniramine Maleate. Therefore, data for Subject #14 was excluded in the ANOVA analysis of Chlorpheniramine Maleate.

- The firm has appropriately calculated Ke for all subjects. There were no PK repeats. The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted repeat values or the average of all determinations, which is appropriate and according to the SOP.

- The reviewer used the CALCKE.SAS program for the statistical analysis. The summary of PK data and results for Hydrocodone are presented in Tables 22-25 and Fig. 1, and for Chlorpheniramine Maleate are presented in Tables 26-29 and Fig. 2.

- The pharmacokinetic parameters and 90% confidence intervals for Hydrocodone and Chlorpheniramine Maleate in plasma calculated by the reviewer agree with firm's calculations.

- The 90% CIs for LAUCt, LAUCi and LCmax parameters for Hydrocodone and Chlorpheniramine Maleate are within the 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The study is **acceptable.**

Table 22. Arithmetic Means and Ratio: Fasting Study (S08-0404) - Hydrocodone (n=30)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	163.90	26.90	166.52	26.13	0.98
AUCI	166.46	26.50	168.80	25.94	0.99
CMAX	14.96	24.68	15.48	24.10	0.97
TMAX	2.75	.	3.00	.	0.92
KE	0.09	18.15	0.09	14.26	1.00
THALF	8.00	18.77	7.88	14.46	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
TMAX VALUES ARE PRESENTED AS MEDIAN

Table 23. Geometric Means and 90% CI - Hydrocodone (n=30)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	158.29	160.55	0.99	95.15	102.15
LAUCI	160.89	162.85	0.99	95.43	102.29
LCMAX	14.56	15.05	0.97	93.12	100.48

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 24. Additional Study Information, Fasting Study – Hydrocodone (n=30)

Root mean square error, AUC0-t	0.080738	
Root mean square error, AUC∞	0.079067	
Root mean square error, Cmax	0.086519	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.98 (0.96 – 1.0)	0.99 (0.96 – 0.99)
Kel and AUC∞ determined for how many subjects?	30	30
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
Measurable drug conc. at 0 hr (>5% of Cmax)	0	0
First measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Table 25. Mean Plasma Concentration – Hydrocodone (n=30)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	3.43	73.21	2.80	63.06	1.23
1	8.77	45.01	8.39	48.58	1.05
1.5	11.19	39.57	11.52	41.00	0.97
2	12.58	34.90	13.16	34.67	0.96
2.5	13.31	30.69	13.95	27.62	0.95
3	13.78	26.94	14.30	24.94	0.96
3.5	13.47	25.27	13.92	23.96	0.97
4	13.10	24.59	13.58	24.27	0.96
4.5	12.60	24.59	12.89	25.01	0.98
5	11.93	25.09	11.99	25.50	0.99
5.5	11.14	24.34	11.20	25.92	1.00
6	10.37	25.37	10.52	26.01	0.99
6.5	9.81	24.99	9.85	24.94	1.00
7	9.15	27.38	9.24	26.39	0.99
7.5	8.69	26.61	8.81	27.64	0.99
8	8.11	26.40	8.22	26.74	0.99
8.5	7.54	26.61	7.57	26.30	1.00
9	7.00	26.75	7.07	26.94	0.99
9.5	6.57	27.05	6.66	26.88	0.99
10	6.33	28.68	6.33	26.92	1.00
11	5.32	29.08	5.35	27.89	0.99
12	4.68	28.16	4.77	28.04	0.98
14	3.84	29.12	3.96	28.78	0.97
16	3.11	31.38	3.16	29.51	0.98
24	1.61	32.03	1.65	31.24	0.98
36	0.57	49.35	0.57	44.29	1.00
48	0.25	88.15	0.26	70.72	0.98
72	0.06	223.81	0.06	170.13	0.91
96	0.03	231.53	0.02	267.53	1.62

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Figure 1. Mean Plasma Concentration – Fasting: Hydrocodone (n=30)

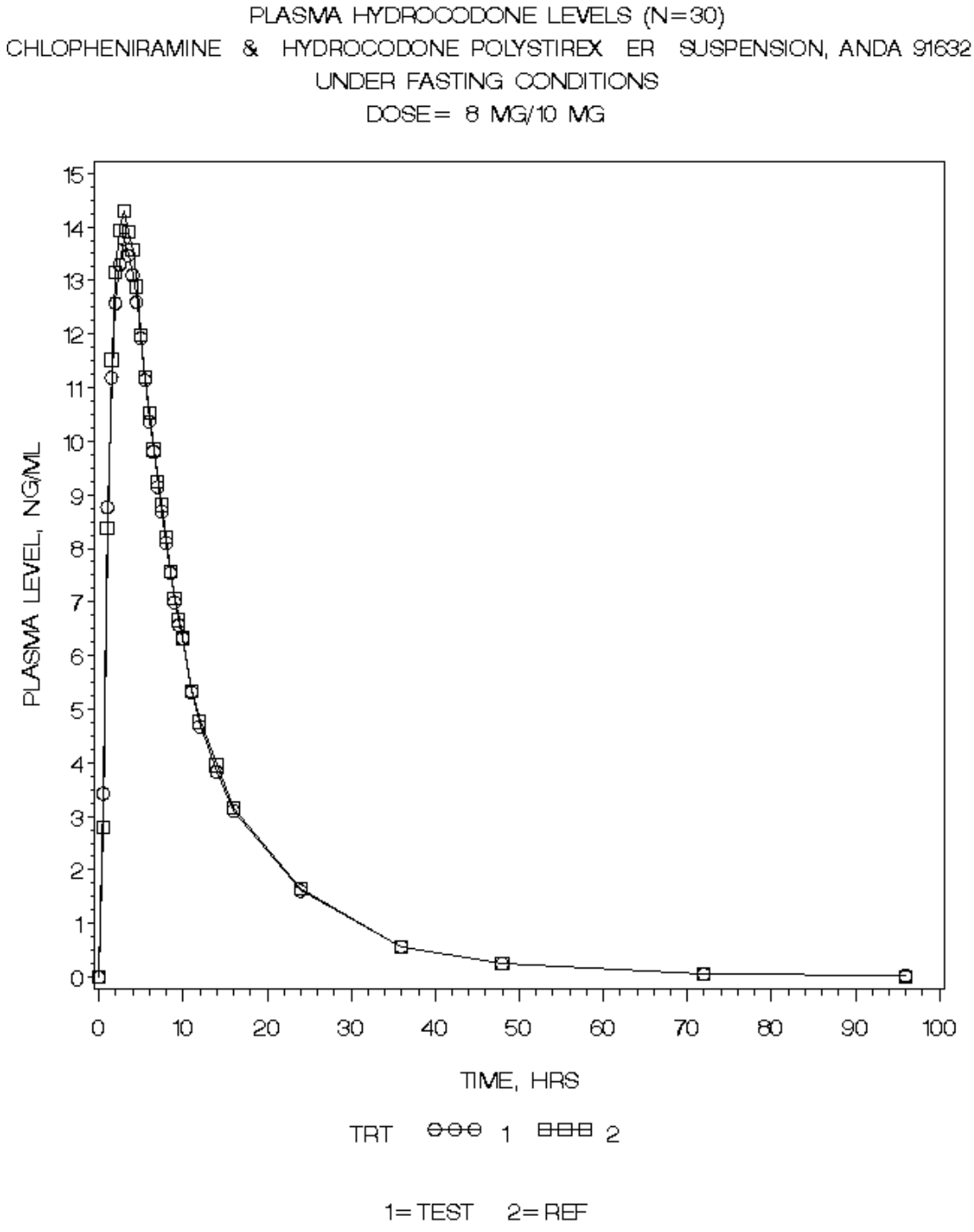


Table 26. Arithmetic Means and Ratio: Fasting Study (S08-0404) - Chlorpheniramine (n=29)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	425.53	41.86	435.75	36.98	0.98
AUCI	483.74	47.98	491.96	43.92	0.98
CMAX	12.70	30.43	13.34	24.32	0.95
TMAX	6.50	.	6.50	.	1.00
KE	0.03	38.55	0.03	34.59	0.99
THALF	27.01	37.86	26.17	35.07	1.03

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
TMAX VALUES ARE PRESENTED AS MEDIAN

Table 27. Geometric Means and 90% CI - Chlorpheniramine (n=29)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	391.48	408.30	0.96	91.37	100.62
LAUCI	434.62	451.65	0.96	91.44	101.26
LCMAX	12.21	12.99	0.94	88.62	99.69

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 28. Additional Study Information, Fasting Study – Chlorpheniramine

Root mean square error, AUC0-t	0.107754	
Root mean square error, AUC∞	0.113920	
Root mean square error, Cmax	0.131487	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.90 (0.75-0.98)*	0.91 (0.73-0.98)
Kel and AUC∞ determined for how many subjects?	29	29
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
Measurable drug conc. at 0 hr (>5% of Cmax)	1 (Sub #14, 16.14%)	0
First measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

*The AUCt/AUCi ratios of subjects below 0.8 were as follows:

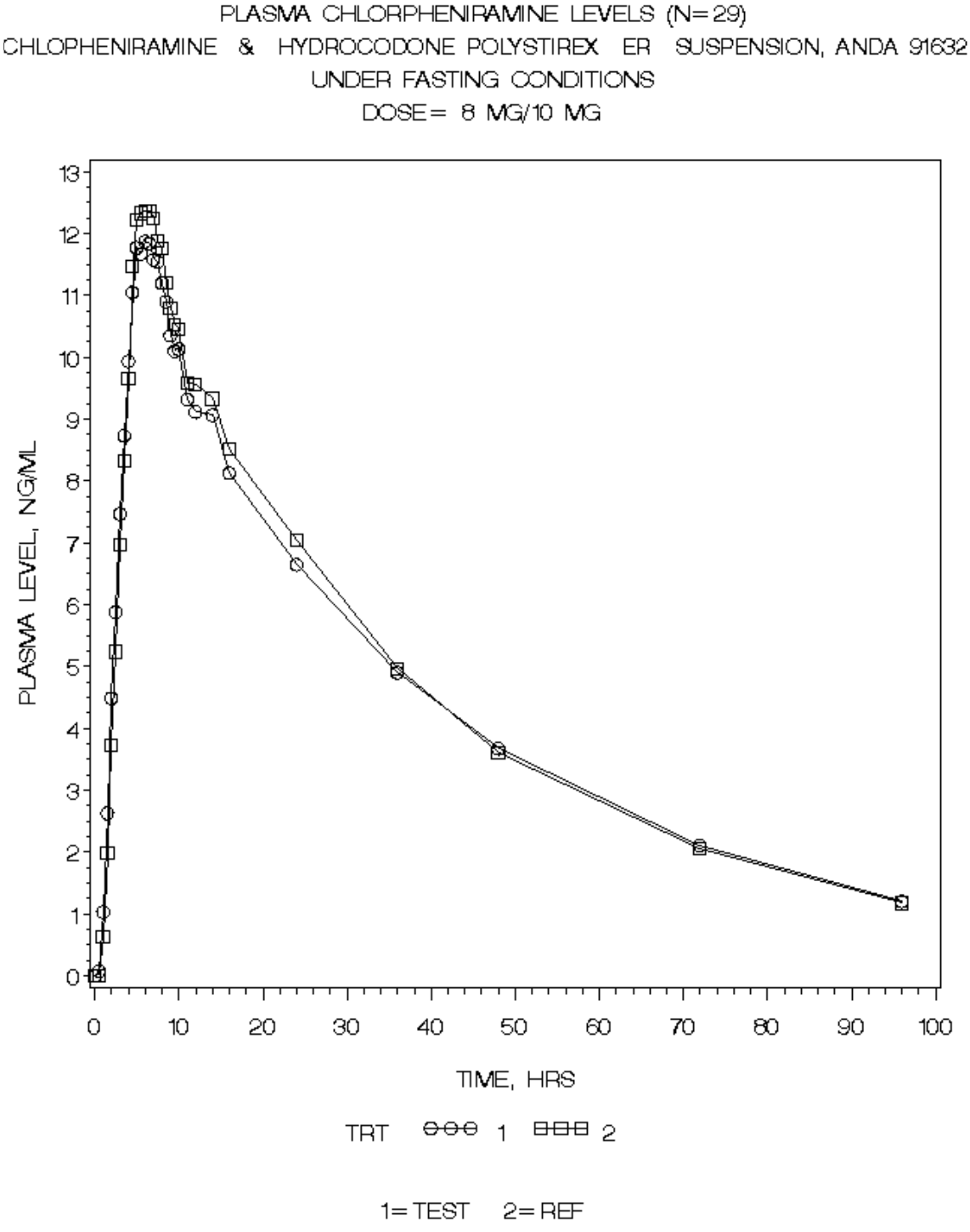
Subject #	Test	Reference
20	0.75	0.73
23	0.77	0.83

Table 29. Mean Plasma Concentration – Chlorpheniramine (n=29)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	0.08	197.49	0.01	374.24	5.53
1	1.04	130.39	0.63	141.33	1.64
1.5	2.63	92.07	1.99	98.91	1.33
2	4.49	79.54	3.74	85.47	1.20
2.5	5.88	70.62	5.24	75.64	1.12
3	7.47	59.27	6.97	60.16	1.07
3.5	8.74	50.89	8.34	52.58	1.05
4	9.94	43.31	9.66	41.42	1.03
4.5	11.05	38.65	11.48	34.98	0.96
5	11.78	33.96	12.23	28.31	0.96
5.5	11.68	30.18	12.33	27.46	0.95
6	11.87	29.42	12.38	25.10	0.96
6.5	11.84	27.40	12.38	22.75	0.96
7	11.58	29.12	12.24	22.58	0.95
7.5	11.54	25.94	11.89	23.84	0.97
8	11.20	26.77	11.77	27.41	0.95
8.5	10.90	26.25	11.21	23.67	0.97
9	10.35	26.85	10.80	23.77	0.96
9.5	10.10	26.49	10.53	26.08	0.96
10	10.13	28.61	10.47	25.24	0.97
11	9.32	28.96	9.59	25.50	0.97
12	9.12	30.85	9.56	26.66	0.95
14	9.07	29.99	9.33	26.49	0.97
16	8.13	32.65	8.53	27.30	0.95
24	6.65	38.97	7.05	36.05	0.94
36	4.91	47.53	4.97	40.52	0.99
48	3.68	52.33	3.62	52.02	1.02
72	2.11	66.61	2.06	62.86	1.02
96	1.21	76.22	1.18	83.44	1.02

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Figure 2. Mean Plasma Concentration – Chlorpheniramine (n=29)



ii. Single-dose Fed Bioequivalence Study

1. Study Design

Table 30 Study Information - Fed Study

Study Number	CRI-00014528/**S08-0405**/R09-0219
Study Title	A Relative Bioavailability Study of Hydrocodone Polistirex ER (Equivalent to 10 mg Hydrocodone Bitartrate) and Chlorpheniramine Polistirex (Equivalent to 8 mg Chlorpheniramine Maleate) per 5 mL Oral Suspension Versus Tussionex® Pennkinetic® ER Oral Suspension Under Fed Conditions
Clinical Site (Name, Address, Phone #)	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301, USA (636)757-7074
Principal Investigator	Ramón Vargas, M.D., M.P.H.
Dosing Dates	Period I: 26 April 2009
	Period II: 10 May 2009
Analytical Site (Name, Address, Phone #)	Cetero Research, 10550 Rockley Road, Suite 150, Houston, TX 77099, 281-495-6996
Analysis Dates	May 25, 2009 to June 02, 2009
Analytical Director	(b) (6) M.S.
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	April 26, 2009 to June 03, 2009 (38 days)

Table 31. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension	Tussionex® Pennkinetic®
Manufacturer	Manufactured by Tris Pharma, Inc.	Manufactured by Celltech Manufacturing, Inc.
Batch/Lot No.	TB-047A	41648
Manufacture Date	04/01/09	N/A
Expiration Date	N/A	05/2009
Strength	hydrocodone polistirex (equivalent to 10 mg hydrocodone bitartrate) and chlorpheniramine polistirex (equivalent to 8 mg chlorpheniramine maleate) per 5 mL	hydrocodone polistirex (equivalent to 10 mg hydrocodone bitartrate) and chlorpheniramine polistirex (equivalent to 8 mg chlorpheniramine maleate) per 5 mL
Dosage Form	ER Oral Suspension	ER Oral Suspension
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency – Hydrocodone	95.6%, 95.6%	97.7%, 96.5%
Potency - Chlorpheniramine	101.9%, 101.9%	100.0%, 100.0%
Content Uniformity (mean, %CV)	N/A	N/A
Dose Administered	1 × 5 mL (hydrocodone polistirex [equivalent to 10 mg hydrocodone bitartrate] and chlorpheniramine polistirex [equivalent to 8 mg chlorpheniramine maleate])	1 × 5 mL (hydrocodone polistirex [equivalent to 10 mg hydrocodone bitartrate] and chlorpheniramine polistirex [equivalent to 8 mg chlorpheniramine maleate])
Route of Administration	Oral	Oral

Table 32. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	30 Subjects were dosed; 28 completed the study; 28 subjects' samples were analyzed.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	AB: 33, 34, 35, 39, 40, 42, 46, 47, 48, 49, 50, 54, 55, 57, 58 BA: 31, 32, 36. 37, 38, 41, 43, 44, 45, 51, 52, 53, 56, 59, 60
Blood Sampling Times	Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 14, 16, 24, 36, 48, 72 and 96 hrs. post-dose

Blood Volume Collected/Sample	6 mL in K2EDTA Vacutainers K3EDTA was never used.
Blood Sample Processing/Storage	After collection, blood samples were cooled; immediately centrifuged; plasma samples were separated, and stored at -20 ^{0}C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects fasted overnight for at least 10 hours prior to drug administration and then for a further 4 hours following drug administration.
Length of Confinement	Subjects were confined to clinical facility from at least 10 hours prior to each drug administration until after the 24-hour blood sample collection.
Safety Monitoring	Subjects were monitored throughout the study.
Drug Specific Information	None
Breakfast	Thirty (30) minutes prior to their assigned dosing time, all subjects began to consume the FDA standardized high fat – high calorie meal. Subjects were required to consume the entire meal prior to drug administration.

Comments on Study Design: The study design is acceptable.

2. Clinical Results

Table 33. Demographics Profile of Subjects Completing the Bioequivalence Study

Fed Bioequivalence Study – Hydrocodone and Chlorpheniramine

CRI-00014528/S08-0405/R09-0219			
		Treatment Groups	
		Test Product N=28[1]	Reference Product N=28[1]
Age (years)	Mean ± SD	31.8 ± 10.3	31.8 ± 10.3
	Range	18 - 57	18 - 57
Age Groups	< 18	-	-
	18 – 39	22 (78.6%)	22 (78.6%)
	40 – 64	6 (21.4%)	6 (21.4%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	17 (60.7%)	17 (60.7%)
	Female	11 (39.3%)	11 (39.3%)
Hispanic or Latino Ethnicity	N	-	-
	A	-	-
	B	2 (7.1%)	2 (7.1%)
	I	-	-

	W IAN	3 (10.7%) 1 (3.6%)	3 (10.7%) 1 (3.6%)
Not Hispanic or Latino Ethnicity	N A B I W	- - 10 (35.7%) - 12 (42.9%)	- - 10 (35.7%) - 12 (42.9%)
BMI	Mean ± SD Range	24.9 ± 3.0 18.1 - 29.9	24.9 ± 3.0 18.1 - 29.9
Other Factors			

[1] Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 34. Dropout Information, Fed Bioequivalence Study

CRI-00014528 (Cetero Research – St. Charles S08-0405)				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
036	Withdrew consent for the study due to family emergency after receiving the reference product	I	No	N/A
049	Withdrew consent for the study due to family emergency after receiving the test product	I	No	N/A

Table 35. Incidence of Adverse Events in Individual Studies - Fed Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	CRI-00014528/S08-0405/R09-0219	
	Test N=29[2]	Reference N=29[2]
	n (%)[3]	n (%)[3]
Investigations		
Aspartate aminotransferase abnormal	1 (3.45%)	-
Blood lactate dehydrogenase abnormal	1 (3.45%)	-
Nervous system disorders		
Dizziness	1 (3.45%)	1 (3.45%)
Headache	1 (3.45%)	-
Total	2 (6.90%)	1 (3.45%)

[1] MedDRA Version 11.1
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%)

Table 36. Protocol Deviations, Fed Bioequivalence Study

Type	Subject No. (Test)	Subject No. (Reference)
Subject was approved for dosing Period I with out of range vital signs by Ramón Vargas, M.D., M.P.H., the Principal Investigator	054	
Subject was approved for dosing Period II with out of range vital signs by Ramón Vargas, M.D., M.P.H., the Principal Investigator	045, 059	033, 058
Period I vital signs obtained outside of the ±30 minute window	033	045, 059
Period I vital signs obtained more than 120 minutes prior to administration of study product to the first study participant	033, 046, 048, 050, 054	031, 052, 053, 060
Period II vital signs obtained outside of the ±30 minute window	041, 045, 053	033
Period II, Hour 36 pulse and respiration not obtained due to staff error	053	
Period II vital signs not obtained due to failure to return to clinic	037	034
Period II adverse event query not obtained due to failure to return to clinic	037	034

Pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times. These deviations did not have an impact on the results.

Comments on Dropouts/Adverse Events/Protocol Deviations: The dropouts were appropriate. Adverse events and deviations were minor and did not compromise the outcome of the study.

3. Bioanalytical Results

Table 37. Assay Validation – Within the Fed BE Study - Hydrocodone

Bioequivalence Study No. S08-0405 Hydrocodone										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.10	0.20	0.40	0.50	1.00	2.00	5.00	20.0	40.0	50.0
Inter day Precision (%CV)	3.1	5.5	3.4	3.3	2.8	3.0	3.4	4.2	2.6	4.7
Inter day Accuracy (%Bias)	3.8	-3.7	-4.2	-5.1	-0.7	-1.1	2.4	2.3	1.9	4.2
Linearity	0.989252 to 0.999491									
Linearity Range (ng/mL)	0.1000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.1000									

Bioequivalence Study No. S08-0405 Hydrocodone			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.2500	3.000	37.50
Inter day Precision (%CV)	13.0	4.7	4.3
Inter day Accuracy (%Bias)	5.8	-1.6	3.1

Table 38. Assay Validation – Within the Fed BE Study - Chlorpheniramine

Bioequivalence Study No. S08-0405 Chlorpheniramine										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.20	0.40	0.80	1.00	2.00	4.00	10.0	40.0	80.0	100
Inter day Precision (%CV)	2.2	4.7	3.2	2.9	2.5	2.7	2.9	3.2	2.1	3.9
Inter day Accuracy (%Bias)	5.5	-6.7	-4.9	-4.8	0.0	-0.7	3.5	3.1	1.6	3.6
Linearity	0.989148 to 0.998591									
Linearity Range (ng/mL)	0.2000 to 50.00									
Sensitivity/LOQ (ng/mL)	0.2000									

Bioequivalence Study No. S08-0405 Chlorpheniramine			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.5000	6.000	75.00
Inter day Precision (%CV)	3.6	3.5	3.7
Inter day Accuracy (%Bias)	4.7	0.1	2.4

Comments on Study Assay Validation: The calibration curve standards and QC samples were prepared in blank plasma fortified with K2EDTA anticoagulant. The assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serial

Comments on Chromatograms: Acceptable

Table 39. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
CET_SOP_04_LBP_006, Version 1	03/18/09	Sample Reanalysis and Reporting Criteria

Table 40. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	There were no PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Repeat Analysis: Fed – Hydrocodone

Table 9 Summary of Repeat Analysis Data for Hydrocodone in Human Plasma

Subject	Period	Time	Custom ID	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for Reported Conc.
0035	2	72h	(b) (4)	(b) (4)	5	1	(b) (4)	32	(b) (4)	1
0042	1	3h			11	2		32		2
0045	1	0h			14	3		32, 32, 32		3
0058	2	96h			27	4		32		2

REASONS FOR REASSAY:
1). EP - Extraction problem (emulsion occurred and sample was very cloudy after extraction)
2). LIS - Low internal standard
3). PIPD - Peak in pre-dose sample
4). HIS - High internal standard

REASONS FOR REPORTED CONC:
1). Good extraction
2). Mean of original and repeat, original and repeat values are within 30%
3). Mean of repeat values used

Repeat Analysis: Fed - Chlorpheniramine

Table 10 Summary of Repeat Analysis Data for Chlorpheniramine in Human Plasma

Subject	Period	Time	Custom ID	Original Conc. ng/mL	Original Curve Number	Reason for Reassay	Reassay Conc. ng/mL	Reassay Curve Number	Reported Conc. ng/mL	Reason for Reported Conc.
0035	2	72h	(b) (4)	(b) (4)	5	1	(b) (4)	32	(b) (4)	1
0042	1	3h			11	2		32		2
0045	2	0h			14	3		32, 32, 32		3
0058	1	6h			27	2		32		2

REASONS FOR REASSAY:
1). EP - Extraction problem (emulsion occurred and sample was very cloudy after extraction)
2). LIS - Low internal standard
3). PIPD - Peak in pre-dose sample

REASONS FOR REPORTED CONC:
1). Good extraction
2). Mean of original and repeat, original and repeat values are within 30%
3). Mean of original and repeat values used

Summary/Conclusions, Study Assays: The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted repeat values or the average of all determinations, which is appropriate and according to the SOP. Sample re-analyses are acceptable.

4. Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis: Study #S08-0405

- The reviewer calculated the 90% confidence intervals for 28 subjects.

- The firm has appropriately calculated Ke for all subjects. There were no PK repeats. The repeat assays had no original values or were within 30% of the original values. Therefore, the firm accepted repeat values or the average of all determinations, which is appropriate and according to the SOP.

- The reviewer used the CALCKE.SAS program for the statistical analysis. The summary of PK data and results for Hydrocodone are presented in Tables 41-44 and Fig. 3, and for Chlorpheniramine Maleate are presented in Tables 45-48 and Fig. 4.

- The pharmacokinetic parameters and 90% confidence intervals for Hydrocodone and Chlorpheniramine Maleate in plasma calculated by the reviewer agree with firm's calculations.

- The 90% CIs for LAUCt, LAUCi and LCmax parameters for Hydrocodone and Chlorpheniramine Maleate are within the 80-125%.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study: The study is **acceptable**.

Table 41. Arithmetic Means and Ratio: Fasting Study (S08-0404) - Hydrocodone (n=28)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	193.29	31.13	195.48	27.80	0.99
AUCI	195.61	30.96	197.63	27.66	0.99
CMAX	15.22	23.05	15.09	18.62	1.01
TMAX	4.50	.	3.75	.	1.20
KE	0.10	18.48	0.09	17.69	1.07
THALF	7.26	16.55	7.72	15.99	0.94

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
TMAX VALUES ARE PRESENTED AS MEDIAN

Table 42. Geometric Means and 90% CI: Fed Study - Hydrocodone (n=28)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	185.07	188.93	0.98	93.72	102.38
LAUCI	187.35	191.09	0.98	93.81	102.47
LCMAX	14.85	14.85	1.00	96.06	104.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 43. Additional Study Information, Fed Study – Hydrocodone (n=28)

Root mean square error, AUC0-t	0.096948	
Root mean square error, AUC∞	0.096870	
Root mean square error, Cmax	0.087028	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.99 (0.97-1.0)	0.99 (0.97-1.0)
Kel and AUC∞ determined for how many subjects?	28	28
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
Measurable drug conc. at 0 hr	0	0
First measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Table 44. Mean Plasma Concentration: Fed Study – Hydrocodone (n=28)

SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
31	2	0.95	0.97	1.07	0.86	1.04	0.96
32	2	0.90	0.88	0.94	0.86	1.34	0.75
33	1	0.84	0.85	0.80	1.00	1.11	0.90
34	1	1.04	1.05	1.02	1.00	0.88	1.14
35	1	0.93	0.95	0.95	1.13	1.12	0.89
37	2	0.91	0.91	0.96	1.20	1.09	0.92
38	2	0.89	0.90	0.99	1.00	1.04	0.96
39	1	1.02	1.03	0.98	0.88	0.97	1.03
40	1	1.15	1.15	1.12	1.43	1.00	1.00
41	2	1.07	1.07	1.32	0.90	1.11	0.90
42	1	1.11	1.10	1.06	1.00	0.95	1.06
43	2	1.03	1.02	0.92	1.00	1.20	0.83
44	2	0.93	0.93	0.96	0.88	0.98	1.02
45	2	1.07	1.07	1.08	1.83	1.08	0.92
46	1	0.90	0.91	1.13	1.13	1.35	0.74
47	1	0.88	0.88	0.95	1.22	1.01	0.99
48	1	0.87	0.87	0.90	0.88	0.98	1.02
50	1	0.84	0.85	0.97	0.89	1.17	0.86
51	2	1.41	1.41	1.38	1.71	0.90	1.12
52	2	0.90	0.89	0.81	1.14	1.19	0.84
53	2	0.98	0.98	1.00	0.90	1.18	0.85
54	1	0.91	0.91	0.80	1.60	1.10	0.91
55	1	0.98	0.97	1.02	1.50	1.09	0.91
56	2	0.81	0.81	0.92	0.71	1.02	0.98
57	1	0.85	0.86	1.06	0.56	1.00	1.00
58	1	0.93	0.92	0.96	1.40	1.22	0.82
59	2	1.37	1.37	1.03	1.50	0.94	1.07
60	2	1.20	1.21	1.09	1.29	0.93	1.07

Figure 3. Mean Plasma Concentration: Fed Study - Hydrocodone (n=28)

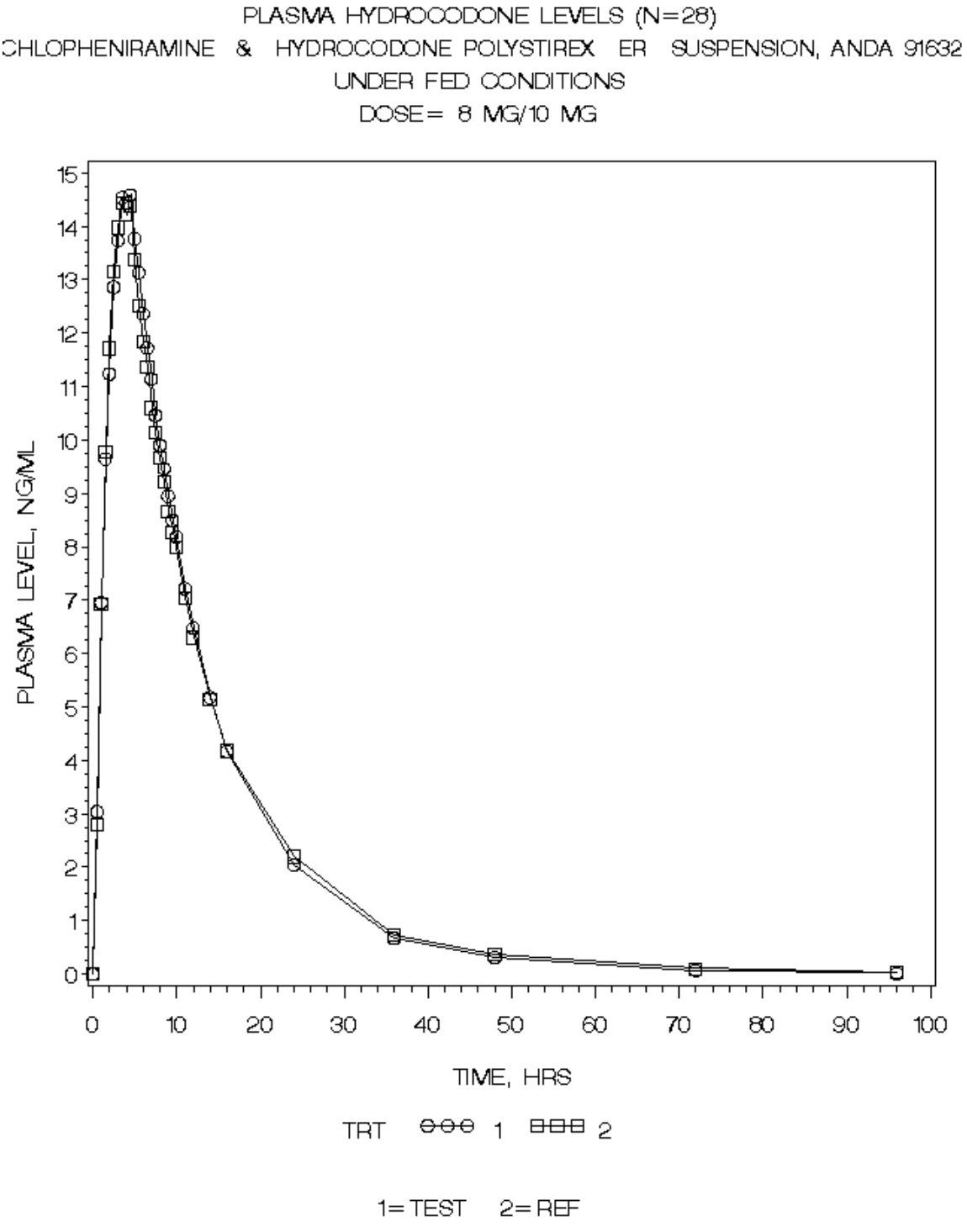


Table 45. Arithmetic Means and Ratio: Fed Study (S08-0405) Chlorpheniramine (n=28)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCT	447.19	50.31	442.05	47.41	1.01
AUCI	500.71	57.57	498.62	54.20	1.00
CMAX	12.17	34.59	12.02	28.69	1.01
TMAX	7.50	.	9.00	.	0.83
KE	0.03	40.55	0.03	34.18	0.96
THALF	25.35	47.45	23.23	40.71	1.09

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
TMAX VALUES ARE PRESENTED AS MEDIAN

Table 46. Geometric Means and 90% CI: Fed Study- Chlorpheniramine (n=28)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
LAUCT	401.32	401.29	1.00	94.95	105.34
LAUCI	437.44	439.71	0.99	93.66	105.67
LCMAX	11.55	11.62	0.99	93.41	105.88

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 47. Additional Study Information: Fed Study – Chlorpheniramine (n=28)

Root mean square error, AUC0-t	0.113919	
Root mean square error, AUC∞	0.132320	
Root mean square error, Cmax	0.137420	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.92 (0.77-0.98)*	0.92 (0.59-0.98)
Kel and AUC∞ determined for how many subjects?	28	28
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
Measurable drug conc. at 0 hr	1 (Sub #45, 2.16%)	0
First measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

*The AUCt/AUCi ratios of subjects below 0.8 were as follows:

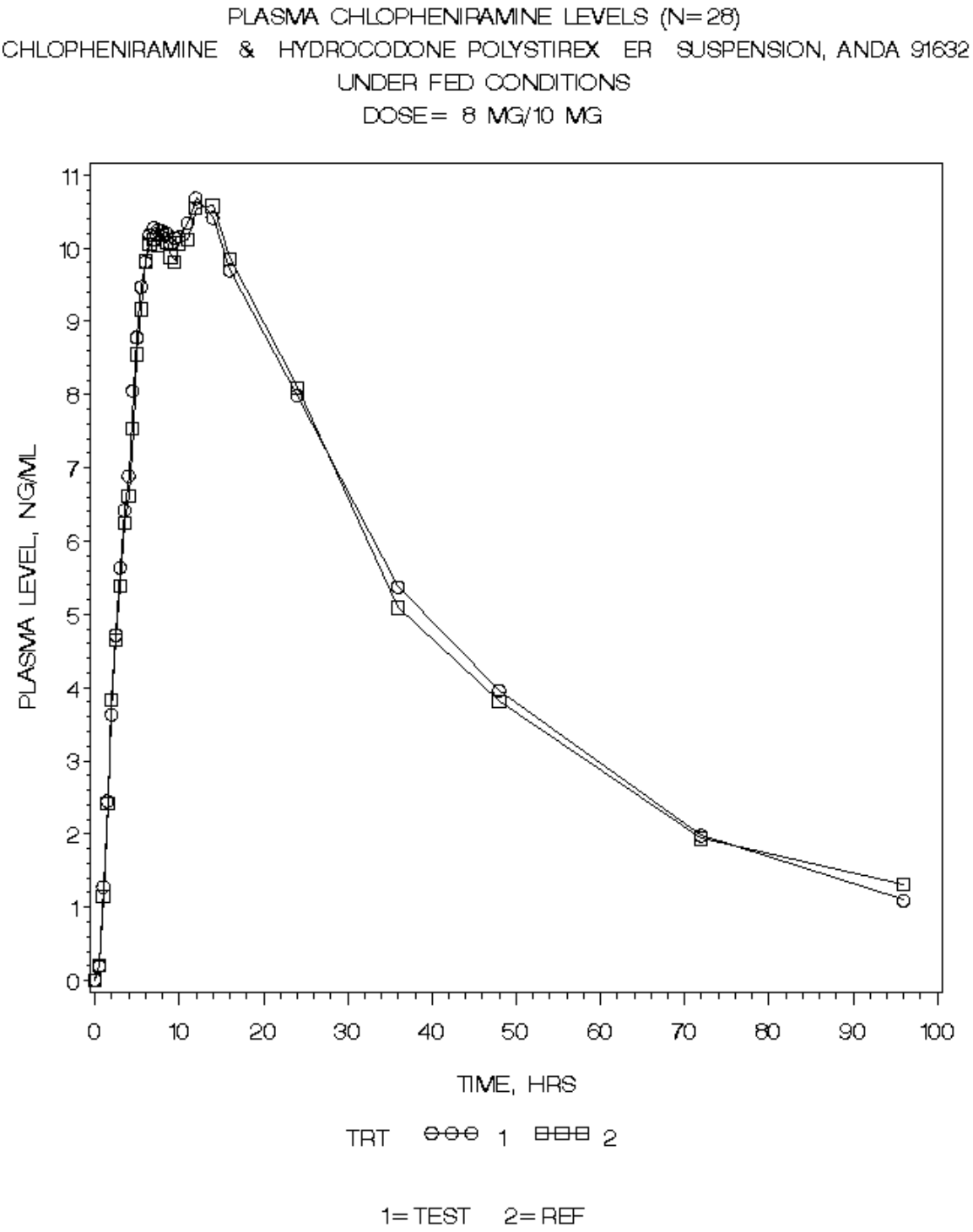
Subject #	Test	Reference
35	0.78	0.77
42	0.77	0.90
31	0.81	0.59

Table 48. Mean Plasma Concentration: Fed Study – Chlorpheniramine (n=28)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.01	529.15	0.00	.	.
0.5	0.20	125.60	0.21	147.12	0.97
1	1.28	67.63	1.15	67.02	1.12
1.5	2.45	52.52	2.43	55.20	1.01
2	3.64	46.88	3.83	46.59	0.95
2.5	4.72	43.97	4.65	42.00	1.02
3	5.64	42.04	5.39	37.00	1.05
3.5	6.42	41.65	6.25	36.89	1.03
4	6.89	39.84	6.62	37.09	1.04
4.5	8.06	46.80	7.55	37.09	1.07
5	8.78	36.69	8.56	33.62	1.03
5.5	9.47	37.73	9.17	30.90	1.03
6	9.81	35.59	9.82	32.32	1.00
6.5	10.18	36.26	10.05	32.43	1.01
7	10.28	36.64	10.11	29.86	1.02
7.5	10.24	35.72	10.04	30.64	1.02
8	10.23	36.24	10.19	28.11	1.00
8.5	10.21	35.34	10.08	30.17	1.01
9	10.05	35.02	9.88	30.02	1.02
9.5	10.14	36.69	9.82	30.16	1.03
10	10.16	37.11	10.07	31.24	1.01
11	10.35	36.66	10.11	32.69	1.02
12	10.68	39.72	10.55	35.15	1.01
14	10.42	39.26	10.58	37.68	0.98
16	9.70	43.07	9.86	38.30	0.98
24	7.99	46.80	8.10	44.67	0.99
36	5.38	58.28	5.09	50.19	1.06
48	3.96	65.40	3.81	65.15	1.04
72	1.98	81.45	1.94	85.40	1.02
96	1.10	109.18	1.31	144.21	0.84

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Figure 4. Mean Plasma Concentration: Fed Study – Chlorpheniramine (n=28)



b. Formulation Data

2.7.1.1 Background and Overview (continue)

Formulation Data

Ingredient	Amount (mg/5mL)	Amount w/v (%)
Sodium Polystyrene Sulfonate	(b) (4)	(b) (4)
Hydrocodone Bitartrate USP	10	
Chlorpheniramine Maleate USP	8	
Purified Water USP	(b) (4)	
Polyvinyl Acetate		
(b) (4)		
Triacetin USP		
Sodium Metabisulfite NF		
Polysorbate 80 NF		
Propylene Glycol USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF		
Ascorbic Acid USP		
Sodium Ascorbate USP		
High Fructose Corn Syrup		
Sucrose NF		
D&C Yellow No. 10		
(b) (4) (Food Starch – Modified)		
(b) (4) Flavor		
(b) (4)		
(b) (4)		

Comments

- MDD for Chlorpheniramine Polistirex and hydrocodone polistirex is 10 mL/day (i.e., 2 x Eq. 8 mg and 10 mg/5 mL). Based on MDD, the daily intake of inactive ingredients and IIG limits are given in the table below.

Excipient	Test Product	IIG Limit and Reference			Acceptable
	Daily Intake, mg	mg/Unit dose	Daily Intake, mg	NDA/ANDA	
Sodium polystyrene sulfonate (b) (4)				(b) (4)	Yes
Polyvinyl Acetate (b) (4)					Yes
(b) (4)					Yes
					Yes
Triacetin USP					Yes
Sodium Metabisulfite NF					Yes
Polysorbate 80 NF					Yes
Propylene Glycol USP					Yes
Methyl Paraben NF					Yes
Propyl Paraben NF					Yes
Xanthan Gum NF					Yes
Ascorbic Acid USP					Yes
Sodium Ascorbate USP					Yes*
High Fructose Corn Syrup (b) (4)					Yes**
Sucrose NF					Yes
D&C Yellow No. 10***					Yes
(b) (4) Food Starch, (b) (4), Modified					Yes
(b) (4) Flavor (b) (4) (b) (4)					Yes
					Yes

(b) (4)

*** D&C Yellow No. 10: The color additive may be safely used for coloring drugs generally in amounts consistent with GMP (21 CFR 74.1710).

- The IIG limits for Sodium ascorbate is (b) (4) than used in the formulation, but a number of drug products have (b) (4) amounts of ascorbic acid and related salts (see the note above). Therefore, the amount of sodium ascorbate should be safe to use.
- The IIG limits for High Fructose Corn Syrup is (b) (4) than used in the formulation, but there are drug products, which contain (b) (4) amounts of fructose or Corn Syrup (see the note above). Therefore, the inactive ingredient should be safe.
- The rest of the excipients used in the formulation are within the IIG limits.

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	None

c. Dissolution Data

Dissolution Review Path	The "Dissolution only" review was not done on this ANDA.

There is no USP method for this product, but there is an FDA-recommended method [495 mL SGF using Paddle at 50 rpm]. See Dissolution method and specifications (NDA)
The firm conducted dissolution testing with a non-FDA-recommended method.

The dissolution data with FDA-method:

The firm did not conduct the dissolution testing using the FDA method.

The dissolution method proposed by the firm:

Apparatus:	2 (Paddle) at 50 rpm
Media:	495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27 M Disodium Phosphate to obtain buffer solution (pH not mentioned)
Temperature:	37 ±0.5ºC
Sampling Time:	1, 3, 6 and 12 hours

Table 49. Summary of In Vitro Dissolution Studies - Hydrocodone

Summary of In Vitro Dissolution Studies – Hydrocodone

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer
	Volume:	5 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications (Hydrocodone)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	3	6	12	Study Report Location
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	28.6	57.6	63.4	68.8	Notebook: QC0214 Page: 085
					Range	(b) (4)				
					%CV	5.54	1.79	1.55	1.52	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	31.8	65.1	72.3	77.6	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	4.92	2.58	1.10	1.02	

Correction: In the above table the firm has not provided volume of 0.1 N HCl. The 5 mL volume mentioned above may be that of the drug product and is not of the dissolution medium. The volume of the dissolution medium should be 895 mL (495 mL for 0.1 N HCl and 400 mL for the phosphate buffer at unknown pH).

Table 50. Summary of In Vitro Dissolution Studies - Chlorpheniramine

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer
	Volume:	5 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications (Chlorpheniramine)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**				**Study Report Location**
						1	**3**	**6**	**12**	
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.6	63.6	70.6	75.2	Notebook: QC0214 Page: 085
					Range	(b) (4)				
					%CV	12.3	2.66	1.89	1.57	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.7	67.0	79.3	85.2	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	6.09	4.68	1.68	1.54	

Correction: In the above table the firm has not provided volume of 0.1 N HCl. The 5 mL volume mentioned above may be that of the drug product and is not of the dissolution medium. The volume of the dissolution medium should be 895 mL (495 mL for 0.1 N HCl and 400 mL for the phosphate buffer at unknown pH).

Multimedia dissolution Testing:

Additionally, dissolution profiles were obtained on 12 dosage units each of the test product and reference product as follows:

Medium:	895 mL, pH 1.2, Buffer pH 4.5, pH 6.8 (USP Buffer Solutions)
Apparatus:	2 (Paddle) at 50 rpm
Sampling Time:	1, 2, 4, 6, 8, 10 and 12 hrs.

The firm has not provided the data summary tables for dissolution at various pHs, and dissolution data on the individual dosage units are not legible. The dissolution profiles in various media are given in Figures 5-10. The firm will be requested to provide the dissolution summary tables, and conduct dissolution testing with the FDA-recommended method.

Figure 5. Dissolution Profile in Acidic Medium, pH 1.2 – Hydrocodone (n=12)

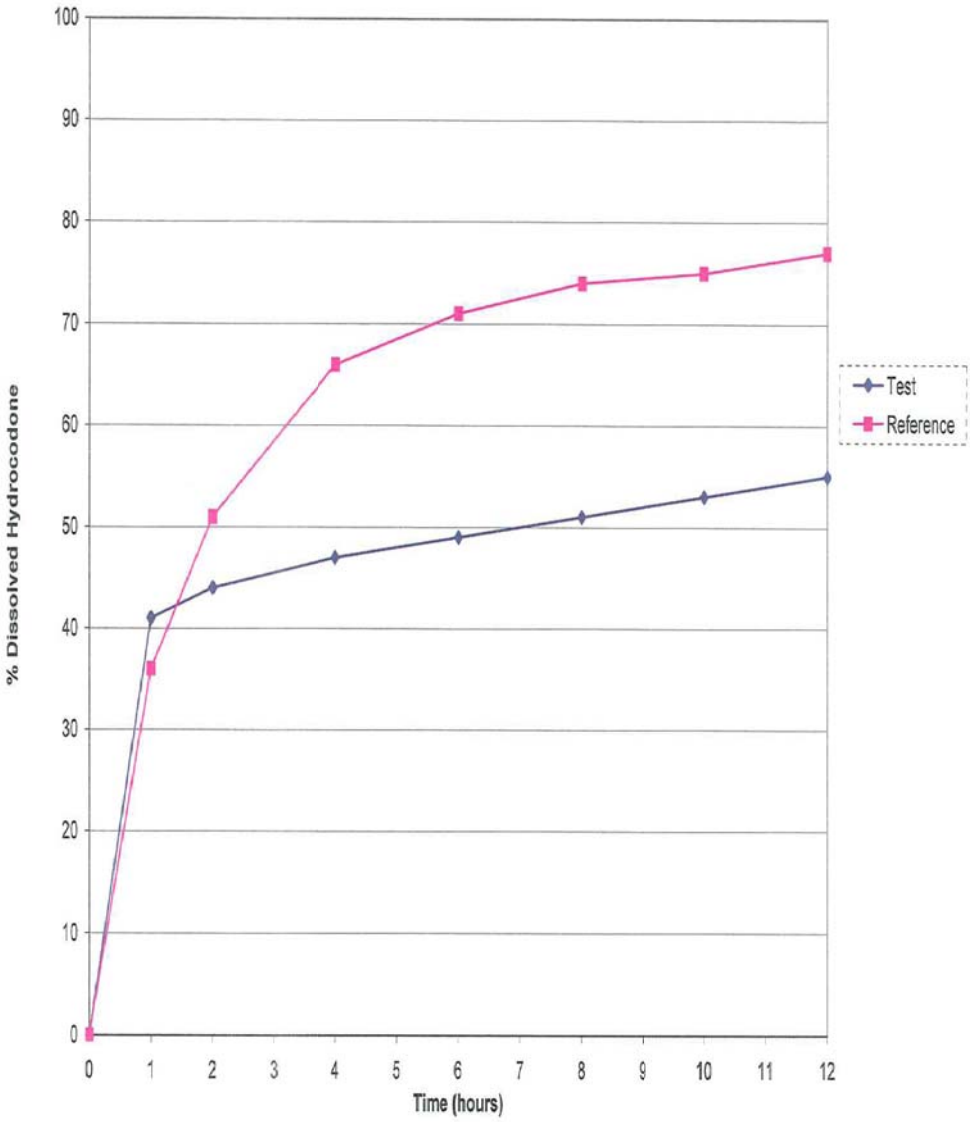


Figure 6. Dissolution Profile in Acidic Medium, pH 1.2 – Chlorpheniramine (n=12)

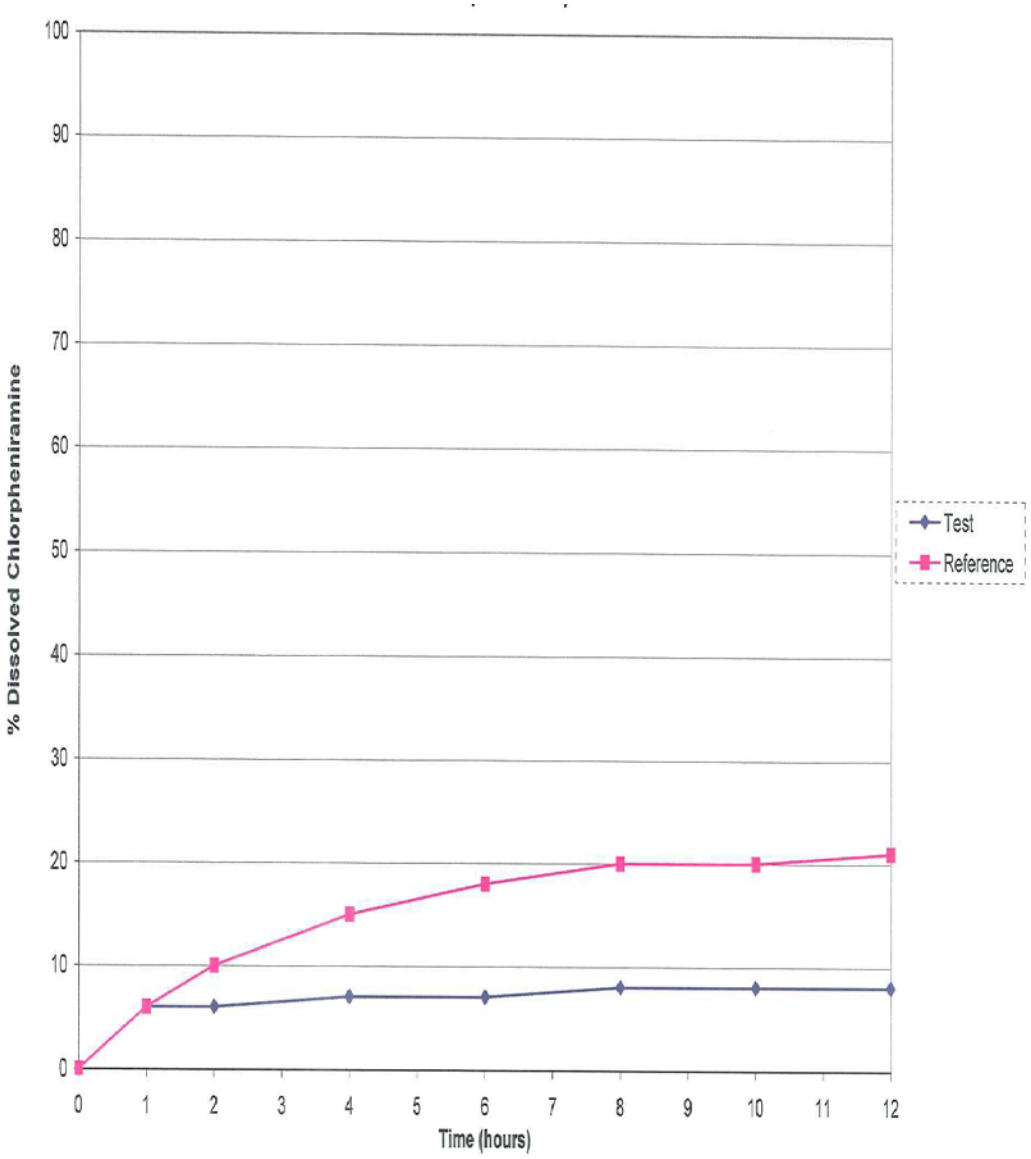


Figure 7. Dissolution Profile in Buffer, pH 4.5 – Hydrocodone (n=12)

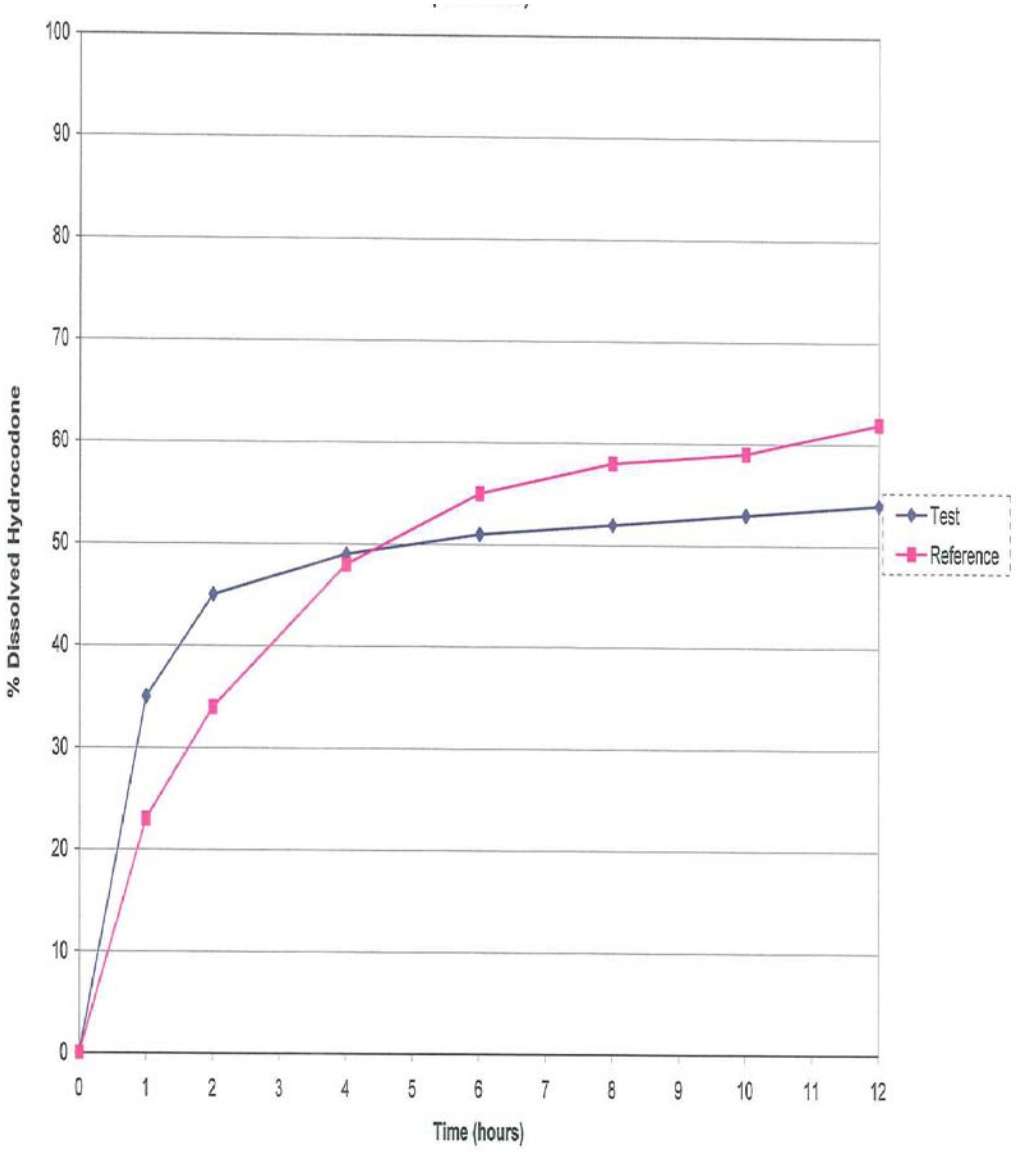


Figure 8. Dissolution Profile in Buffer, pH 4.5 - Chlorpheniramine (n=12)

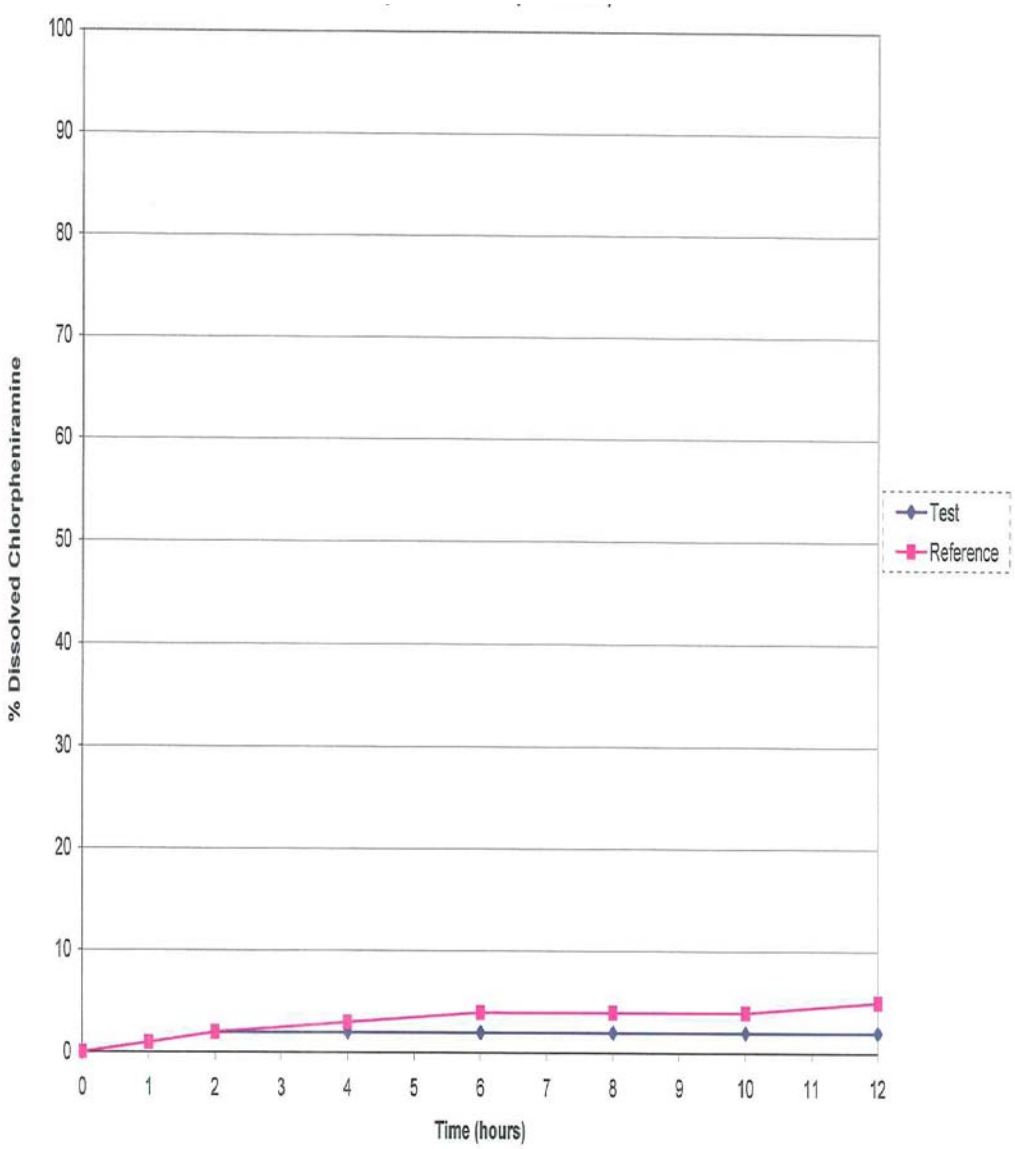


Figure 9. Dissolution Profile in Buffer, pH 6.8 – Hydrocodone (n=12)

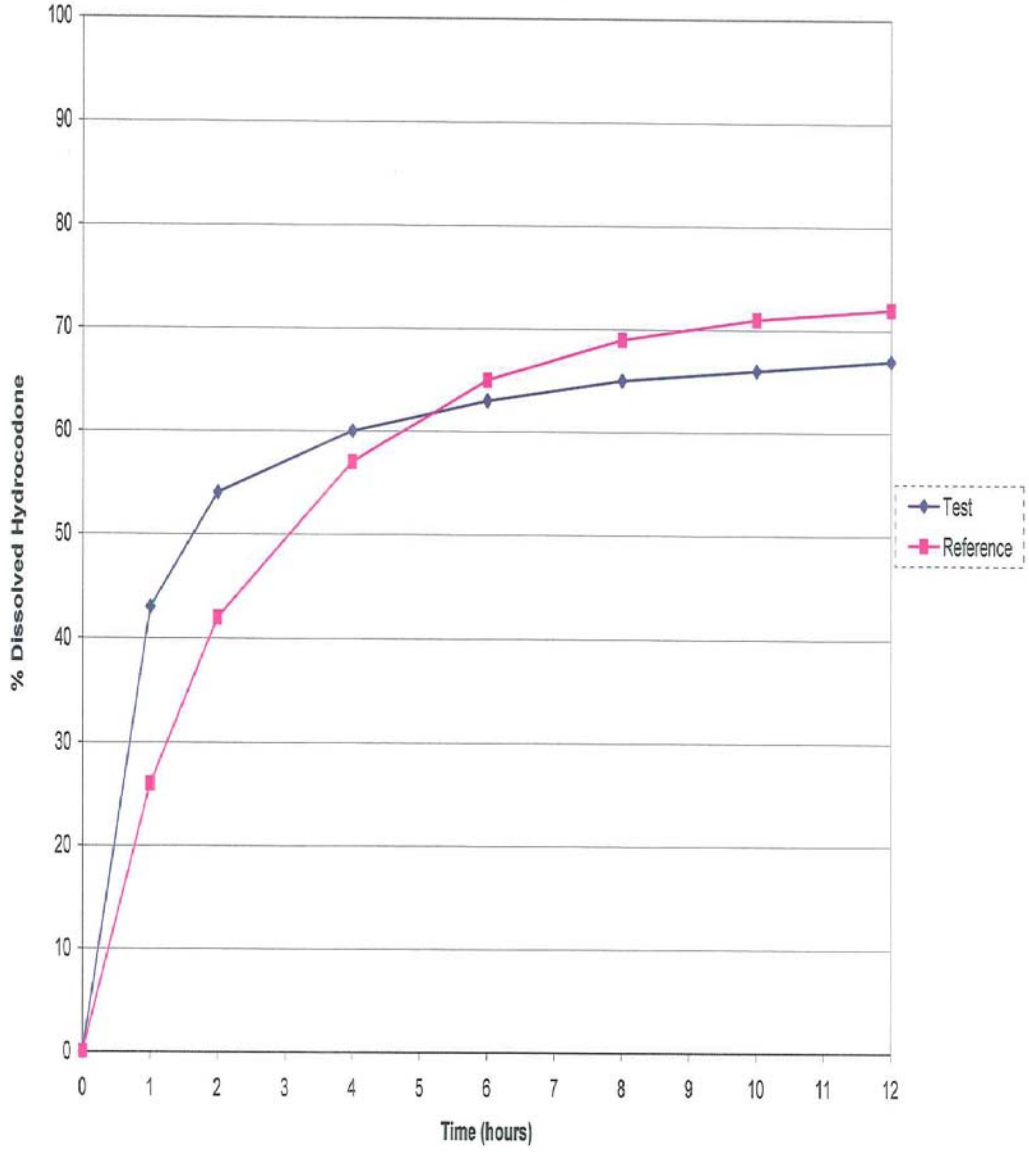
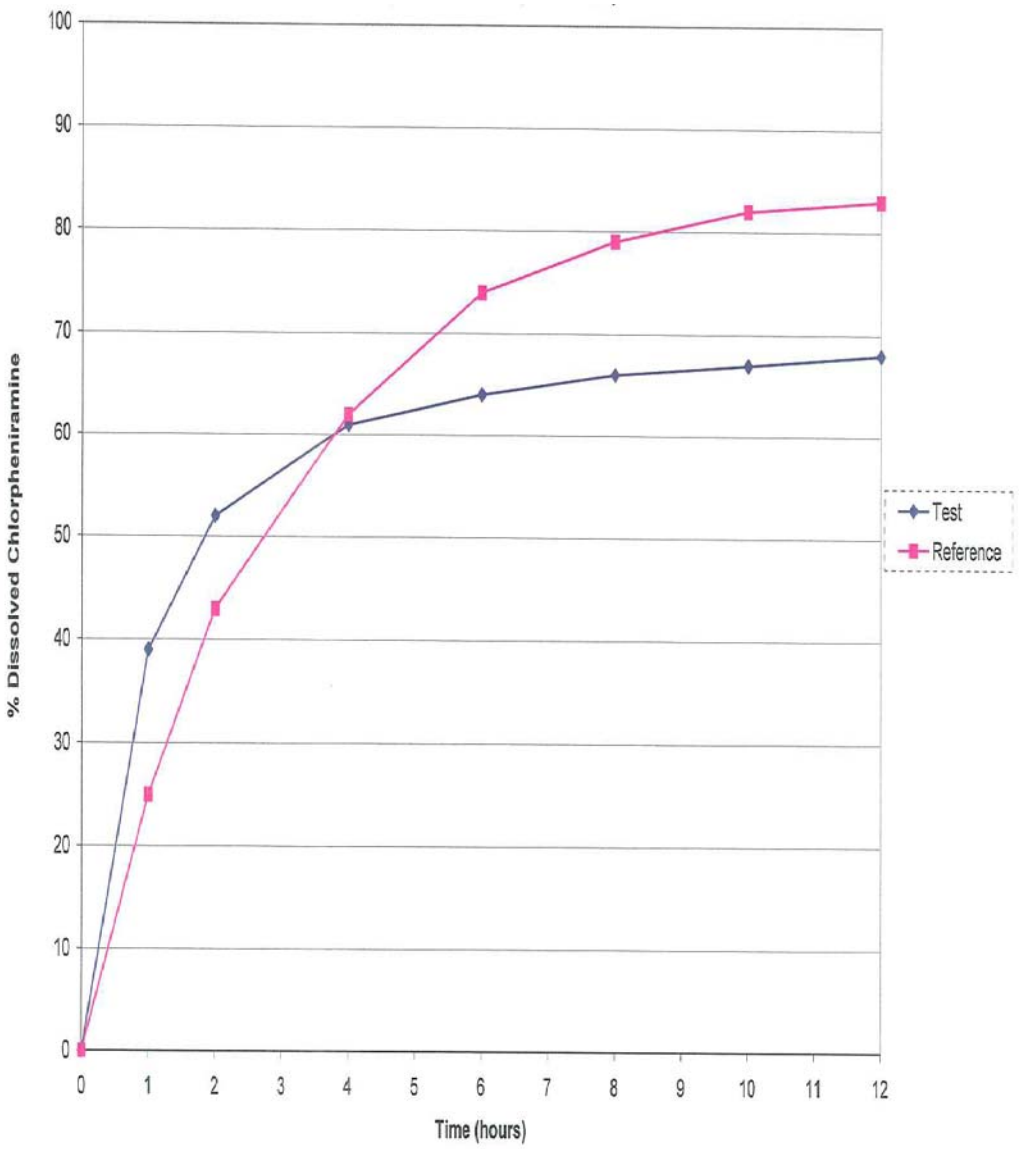


Figure 10. Dissolution Profile in Buffer, pH 6.8 - Chlorpheniramine (n=12)



d. Consult Reviews

None

e. SAS Output

(b) (4)

Following this page, 97 pages withheld in full (b)(4)

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have proposed the following dissolution testing method for your product:

   Apparatus: 2 (Paddle) at 50 rpm
   Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH not mentioned)
   Temperature: 37 ±0.5°C
   Sampling Time: 1, 3, 6 and 12 hours

   However, at the last sampling time point of 12 hours, your test product did not reach dissolution of at least 80% of either component, hydrocodone or chlorpheniramine. Please repeat the dissolution testing using your proposed method, and sample until at least 80% of both components is dissolved. Please also provide the pH of the medium after you add 400 mL of 0.27 M disodium phosphate to 495 mL of 0.1 N HCl.

2. In addition, please conduct dissolution testing using the following FDA-recommended method for the test and reference products for comparative evaluation of both methods:

   Medium: 495 mL Simulated Gastric Fluid (SGF) at 37°C
   Apparatus: USP 2 (Paddle) at 50 rpm
   Sampling Time: 1, 3, 8, 24 hours or until 80% of the each drug in the dosage form is dissolved

3. You have conducted dissolution testing in other media, viz., buffers at pH 1.2, 4.5 and 6.8. However, you have not provided the summary tables of dissolution data (testing date, mean dissolution, range, %CV, etc. for the test and reference products) in eCTD format. Please provide the summary tables. Additionally, the dissolution data on the individual dosage units are not legible. Please provide a legible copy of these dissolution testing results.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

g. Outcome Page

CC: ANDA: 91632

4.8. COMPLETED ASSIGNMENT FOR 91632 ID: 10076

Reviewer: Shrivastava, Surendra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
10076	7/13/2009	Dissolution Data	Dissolution Review	0	0	Edit	Delete
10076	7/13/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
10076	7/13/2009	Bioequivalence Study	Fed Study	1	1	Edit	Delete
				Bean Total:	2		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
02/03/2010

SHRINIWAS G NERURKAR
02/03/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/04/2010

DIVISION OF BIOEQUIVALENCE REVIEW - AMENDMENT

ANDA No.	091632		
Drug Product Name	Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension		
Strength(s)	Eq. 8 mg and 10 mg/5 mL		
Applicant Name	Tris Pharma, Inc.		
Address	2033 Route 130, Monmouth Junction, NJ 08852		
Applicant's Point of Contact	W. Scott Groner, Dir. Reg. Affairs and Compliance		
Contact's Telephone Number	732-940-0358		
Contact's Fax Number	732-940-0374		
Original Submission Date(s)	July 13, 2009		
Submission Date(s) of Amendment(s) Under Review	**March 4, 2010**		
Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	S08-0404	S08-0405	
Study Type (s)	Fasting	Fed	
Strength (s)	Eq. 8 mg and 10 mg/5 mL		
Clinical Site	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301		
Clinical Site Address	See above		
Analytical Site	Cetero Research 10550 Rockley Road Suite 150 Houston, TX 77099		
Analytical Site Address	See above		
Dissolution Testing Site	Tris Pharma, Inc., 2033 Route 130, Monmouth Junction, NJ		
DSI Inspection Status	Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4) which **has not been completed**. Analytical Site Cetero Research, Houston, TX: Routine Inspection for NDA (b) (4) was completed on (b) (4) – Satisfactory.		
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	N/A		
DSI REPORT RESULT	See above		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
Supporting Document # 1	**DISSOLUTION**	Eq. 8 mg CP and 10 mg HP/5 mL	**INADEQUATE**
Supporting Document # 1	**FASTING STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
ADEQUATE	**FED STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
	PERMEABILITY STUDY	N/A	N/A
	SOLUBILITY STUDY	N/A	N/A

1. EXECUTIVE SUMMARY

This application references Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (RLD Tussionex Pennkinetic®, NDA 19111, UCB Inc., Approved 12/31/1987). The firm submitted one fasting and one fed bioequivalence (BE) study on July 13, 2009. There was no "dissolution only" review on this ANDA. According to the earlier review ("full-ANDA" and dissolution testing) the **fasting and fed BE study were acceptable** and the DBE informed the firm 3 deficiencies that pertained to the dissolution testing [**DARRTS for 91632 SHRIVASTAVA, SURENDRA P 02/04/2010 N/A 02/04/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive**].

.In this amendment, the firm is responding to 3 deficiencies. The firm has satisfactorily responded to the 3 deficiencies. It has shown that i) the FDA method is not suitable for its product, ii) multimedia dissolution testing is acceptable and iii) the DBE accepts its proposed method but recommends more appropriate specifications than the specifications proposed by the firm.

Apparatus:	2 (Paddle) at 50 rpm
Media:	495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature:	37 ±0.5ºC
Sampling Time:	1, 3, 6 and 12 hours

The firm proposed following specifications for both components

1 Hr. - 3 Hrs.	(b) (4)
6 Hrs.	
12 Hrs	

The DBE recommends following specifications based on the dissolution of the fresh lot (earlier review) and confirmed by the dissolution in this amendment which the product will meet at the L1 level. The limits were based on the IVIVC Guidance recommendation (under "Setting Dissolution Specifications) for the fresh lot.

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

The BE studies were acceptable. The dissolution testing is now acceptable. The firm should acknowledge the dissolution testing method and specification.

Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4) which has not been completed.

Analytical Site Cetero Research, Houston, TX: Routine Inspection for NDA (b) (4) was completed on (b) (4) – Satisfactory.

The application is in**complete (inadequate) pending firm's acknowledgement of the dissolution method and specification as well as inspection of the Clinical Site.**

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1.Drug Product Information

Test Product	Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-Release **suspension**, 8 mg/10 mg (equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate) per 5 mL suspension
Reference Product	Tussionex® Pennkinetic® (chlorpheniramine polistirex and hydrocodone polistirex) Extended-Release **Oral Suspension**, equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate per 5 mL suspension
RLD Manufacturer	UCB Inc.
NDA/ANDA No.	19-111
RLD Approval Date	December 31, 1987
Indication	Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.
Dosing Regimen	Every 12 hours

3.2.PK/PD Information

See the original Review (DARRTS for 091632 SHRIVASTAVA, SURENDRA P 02/04/2010 N/A 02/04/2010 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive].

NOT FOR RELEASE UNDER F.O.I.

Dissolution method and specifications (NDA) [1]

Medium:	Simulated Gastric Fluid (SGF) at 37ºC ± 0.5ºC
Volume:	495 mL
Apparatus:	USP apparatus II (Paddle)
Speed:	50 rpm
FDA-Recommended Specifications:	
• Hydrocodone	1 hour: (b) (4) 3 hours: 8 hours: 24 hour
• Chlorpheniramine	1 hour: (b) (4) 3 hours: 8 hours: 24 hour

3.3.Contents of Submission

Deficiency Response.

3.4. Dissolution Method

Source of Method		Firm
Medium		Acidic medium at 0.1 N HCl for 1 hour followed by phosphate buffer until 12 hrs., pH 6.8
Volume (mL)		495 and 895 mL
USP Apparatus type		I1 (Paddle)
Rotation (rpm)		50 rpm
Firm's proposed Specifications for both components		1 Hr. - (b) (4) 3 Hrs. 6 Hrs. 12 Hrs
FDA-recommended specifications	Hydrocodone:	1 hr 3 hr 6 hr 12 hr
	Chlorpheniramine:	1 hr 3 hr 6 hr 12 hr
F2 metric calculated?		Yes
If no, reason why F2 not calculated		N/A
Is method acceptable?		Acceptable
If not then why?		The firm has used its own method. It has also conducted dissolution testing using the FDA-recommended method.

[1] OCPB Review of NDA 19-111, CHOI, YOUNG M 02/01/2002 N/A 02/01/2002 Archive, http://darrts fda.gov:7777/darrts/ViewDocument?documentId=090140af8013dbf7

3.5. Deficiencies, Firm's Response and Conclusion

DEFICIENCY-1: *You have proposed the following dissolution testing method for your product:*

Apparatus:	*2 (Paddle) at 50 rpm*
Media:	*495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH not mentioned)*
Temperature:	*37 ±0.5°C*
Sampling Time:	*1, 3, 6 and 12 hours*

However, at the last sampling time point of 12 hours, your test product did not reach dissolution of at least 80% of either component, hydrocodone or chlorpheniramine. Please repeat the dissolution testing using your proposed method, and sample until at least 80% of both components is dissolved. Please also provide the pH of the medium after you add 400 mL of 0.27 M disodium phosphate to 495 mL of 0.1 N HCl.

Firm's Response:

Tris acknowledges that at the last sampling time point of 12 hours our test did not reach dissolution of at least 80% of either component, hydrocodone or chlorpheniramine. As per FDA's request, Tris has repeated the dissolution testing using the proposed method and sample until at least 80% of both components is dissolved. Tris also provided the pH of 6.8 for the medium after adding 400 mL of 0.27M disodium phosphate to 495 mL of 0.1 N HCl. Please note after 24-hours the dissolution rate has reached plateau. For updated dissolution table, refer Module 5.3.1.3 "In-Vitro-In-Vivo Correlation Study Reports" and Module 5.3.1.3 additional "raw data dissolution profile study".

The firm's additional dissolution data with extended hours of dissolution testing are provided below in Table 1. The dissolution data from the earlier review are shown in Table 2 (hydrocodone) and Table 3 (chlorpheniramine).

Table 1. Hydrocodone and Chlorpheniramine: Test (Firm's Method)

Dissolution Testing Date for Test Product: 2/24/2010

Sampling Time	Test Product			Reference Product		
	Mean	%CV	Range	Mean	%CV	Range
Hydrocodone						
Hours	Lot No. TB 047A			Lot No. 41648		
1	26	5.2	(b) (4)	31.8	4.92	(b) (4)
3	59	2.6		65.1	2.58	
6	68	1.8		72.3	1.10	
12	74	1.8		77.6	1.02	
18	76	1.6		N/A		
24	78	1.8		N/A		
30	80	1.7		N/A		
36	81	1.7		N/A		
f2 metric				64.39		
Chlorpheniramine						
Hours	Lot No. TB 047A			Lot No. 41648		
1	0	0.0	(b) (4)	0.7	6.09	(b) (4)
3	55	3.3		67.0	4.68	
6	62	2.2		79.3	1.68	
12	69	1.8		85.2	1.54	
18	71	1.6		N/A		
24	73	2.4		N/A		
30	77	1.7		N/A		
36	77	2.0		N/A		
f2 metric				43.77		

Table 2. Summary of In Vitro Dissolution Studies – Hydrocodone

Dissolution Testing Date for Test Product: 4/22/2009

Summary of In Vitro Dissolution Studies – Hydrocodone

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer
	Volume:	5 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications (Hydrocodone)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	3	6	12	Study Report Location
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	28.6	57.6	63.4	68.8	Notebook: QC0214 Page: 085
					Range	(b) (4)				
					%CV	5.54	1.79	1.55	1.52	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	31.8	65.1	72.3	77.6	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	4.92	2.58	1.10	1.02	

F2 Value: 56.14

Table 3. Summary of In Vitro Dissolution Studies - Chlorpheniramine

Dissolution Testing Date for Test Product: 4/22/2009

Dissolution Conditions		**Apparatus:**			USP II (Paddle)					
		Speed of Rotation:			50 rpm					
		Medium:			0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer					
		Volume:			5 mL					
		Temperature:			37 ºC ± 0.5 ºC					
Firm's Proposed Specifications (Chlorpheniramine)		1 hour 3 hour 6 hour 12 hour [redacted] (b) (4)								
Dissolution Testing Site (Name, Address)		Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852								
Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**				**Study Report Location**
						1	**3**	**6**	**12**	
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.6	63.6	70.6	75.2	Notebook: QC0214 Page: 085
					Range	[redacted] (b) (4)				
					%CV	12.3	2.66	1.89	1.57	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.7	67.0	79.3	85.2	Notebook: QC0215 Page: 095
					Range	[redacted] (b) (4)				
					%CV	6.09	4.68	1.68	1.54	

F2 Value: 58.01

Reviewer's Comments

- The firm was successful in showing that its product reaches dissolution plateau from 12 hours to 36 hours for both components without achieving 80% dissolution for every tablets of 12 tablets.

- The firm's data are summarized in Table 1. Similarity Factor, F2 Value, for hydrocodone is >50, but for chlorpheniramine is <50 (43.77).

Conclusion: Firm's response is acceptable. However, based on the available data, the dissolution specification is modified. The firm should acknowledge the acceptance of dissolution method and specifications as follows:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5ºC
Sampling Time: 1, 3, 6 and 12 hours
Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

DEFICIENCY-2: *In addition, please conduct dissolution testing using the following FDA-recommended method for the test and reference products for comparative evaluation of both methods:*

Medium: *495 mL Simulated Gastric Fluid (SGF) at 37ºC*
Apparatus: *USP 2 (Paddle) at 50 rpm*
Sampling Time: *1, 3, 8, 24 hours or until 80% of the each drug in the dosage form is dissolved*

Firm's Response:

Tris has conducted as per the FDA's recommended method, a dissolution testing for the test and the reference products for comparative evaluation of both methods. Refer Module 5.3.1.3 "In-Vitro-In-Vivo Correlation Study Reports" and Module 5.3.1.3 additional "raw data dissolution profile study".

The firm has provided the dissolution in both media, SGF with and without enzyme. Data are provided below. The Test vs. Reference comparisons are provided in Tables 4 and 5. The similarity factor F2 values are >50 except for hydrocodone in SGF without enzyme medium (see Table 5).

Table 4. Hydrocodone and Chlorpheniramine: Reference (FDA Method, SGF with Enzyme)

Sampling Time	Test Product			Reference Product		
	Mean	%CV	Range	Mean	%CV	Range
Hydrocodone						
Hours	Lot No. TB 047A			Lot No. 53087, Exp 11/2011		
1	27	8.4	(b) (4)	24	10.4	(b) (4)
3	36	2.2		37	2.4	
8	44	2.5		49	5.2	
12	47	2.5		54	6.2	
18	51	2.8		60	6.1	
24	53	2.1		63	7.0	
30	57	2.5		67	5.1	
36	58	2.3		70	6.5	
f2 metric				54.74		
Chlorpheniramine						
Hours	Lot No. TB 047A			Lot No. 53087, Exp 11/2011		
1	3	12.3	(b) (4)	2	31.1	(b) (4)
3	6	9.5		4	12.3	
8	9	7.5		9	12.8	
12	11	6.4		12	14.6	
18	12	6.4		16	13.4	
24	14	6.8		19	15.9	
30	17	6.6		23	6.9	
36	18	6.2		26	12.6	
f2 metric				67.82		

Table 5. Hydrocodone and Chlorpheniramine: Reference (FDA Method, SGF without Enzyme)

Sampling Time	Test Product			Reference Product		
	Mean	%CV	Range	Mean	%CV	Range
Hydrocodone						
Hours	**Lot No. TB 047A**			**Lot No. 53087, Exp 11/2011**		
1	32	8	(b) (4)	34	1.5	(b) (4)
3	40	8.5		46	6.4	
8	52	6.4		65	3.4	
12	56	4.7		69	2.6	
18	60	3.7		73	1.8	
24	62	2.6		76	1.9	
30	64	1.8		79	1.7	
36	66	1.9		80	1.8	
f2 metric				**45.85**		
Chlorpheniramine						
Hours	**Lot No. TB 047A**			**Lot No. 53087, Exp 11/2011**		
1	1	28.9	(b) (4)	3	15.1	(b) (4)
3	1	0		3	13.0	
8	1	0		5	9.0	
12	1	0		5	0	
18	1	28.9		5	5.8	
24	1	28.9		5	7.8	
30	1	0		5	9.8	
36	1	49.2		6	9.2	
f2 metric				**70.51**		

Conclusion: Firm's response is acceptable. The DBE agrees that the current FDA-recommended method (from NDA) is not suitable for the formulation in this ANDA 091632.

DEFICIENCY-3: *You have conducted dissolution testing in other media, viz., buffers at pH 1.2, 4.5 and 6.8. However, you have not provided the summary tables of dissolution data (testing date, mean dissolution, range, %CV, etc. for the test and reference products) in eCTD format. Please provide the summary tables. Additionally, the dissolution data on the individual dosage units are not legible. Please provide a legible copy of these dissolution testing results.*

Firm's Response:

Please note that the summary tables of dissolution data (testing date, mean dissolution, range, %CV, etc) were provided by Tris, during the original submission in Module 5.3.1.3 "In-vitro In-vivo Correlation". During the review of original submission, Tris noted an error in the chlorpheniramine dissolution graph provided during the submission. The graph was revised and updated to correct the error and is provide. Refer, Module 5.3.1.3 for updated dissolution summary tables.

Firm's data are provided below.

5.0 Dissolution Profile Study Test 1:

Apparatus: USP Type II (Paddle)
Speed: 50 RPM
Medium: buffer pH 1.2
Volume: 895 mL
Sampling times: 1, 2, 4, 6, 8, 10 and 12 hours

Preparation of pH 1.2 *(Reference: USP – Volumetric Solutions and Reagents: Buffer Solutions):*

1. Preparation of 0.2 M HCl; dilute 51 mL of hydrochloric acid with water to 3000 mL.
2. Preparation of 0.2 M Potassium Chloride (KCl) solution; dissolve 29.82 g of Potassium Chloride in water and dilute with water to 2000 mL.
3. Preparation of buffer pH 1.2; add 1500 mL of Potassium Chloride solution and 2550 mL of 0.2 M HCl in a suitable container and dilute to 6000 mL with water.

Dissolution Profile

Time	Test Product (n = 12) MG 07/10/09 Hydrocodone TB-047A	Reference Product (n = 12) Hydrocodone 41648
1-hour	Average = ~~39 45%~~ 41%. Range = (b) (4)	Average = 36%. Range = (b) (4)
2-hours	Average = 44% Range = (b) (4)	Average = 51%. Range = (b) (4)
4-hours	Average = 47%. Range = (b) (4)	Average = 66%. Range = (b) (4)
6-hours	Average = 49%. Range = (b) (4)	Average = 71%. Range = (b) (4)
8-hours	Average = 51%. Range = (b) (4)	Average = 74% Range = (b) (4)
10-hours	Average = 53%. Range = (b) (4)	Average = 75%. Range = (b) (4)
12-hours	Average = 55%. Range = (b) (4)	Average = 77% MC 07/10/09 Range = (b) (4)

Notebook Ref.: QC0213/24; QC0228/69

Transcribed By: (b) (6) Date: 07/10/09

Verified By: Date: 07/10/09

F2 Value (T vs. R): 36.52

5.0 Dissolution Profile Study Test 1 (continue):

Dissolution Profile				
Time	**Test Product (n = 12)**		**Reference Product (n = 12)**	
	Chlorpheniramine TB-047A		**Chlorpheniramine** 41648	
1-hour	Average = 6%	Range = (b) (4)	Average = 6%	Range = (b) (4)
2-hours	Average = 6%	Range = (b) (4)	Average = 10%	Range = (b) (4)
4-hours	Average = 7%	Range = (b) (4)	Average = 15%	Range = (b) (4)
6-hours	Average = 7%	Range = (b) (4)	Average = 18%	Range = (b) (4)
8-hours	Average = 8%	Range = (b) (4)	Average = 20%	Range = (b) (4)
10-hours	Average = 8%	Range = (b) (4)	Average = 20%	Range = (b) (4)
12-hours	Average = 8%	Range = (b) (4)	Average = 21%	Range = (b) (4)

Notebook Ref.: QC0213/24; QC0228/69

Transcribed By: (b) (6) Date: 07/10/09

Verified By: Date: 07/10/09

F2 Value (T vs. R): 50.56

6.0 Dissolution Profile Study Test 2:

Apparatus: USP Type II (Paddle)
Speed: 50 RPM
Medium: buffer pH 4.5
Volume: 895 mL
Sampling times: 1, 2, 4, 6, 8, 10 and 12 hours

Preparation of pH 4.5*(Reference: USP – Volumetric Solutions and Reagents: Buffer Solutions)*

1. Preparation of 2 N Acetic Acid; Add 11.6 mL of glacial acetic acid to sufficient water to make 100 mL after cooling to room temperature.
2. Preparation of buffer pH 4.5; Accurately weigh and transfer about 17.94 g of Sodium Acetate trihydrate to a suitable container. Add 84 mL of 2 N Acetic Acid and dilute with water to 6000 mL and mix.

Dissolution Profile

Time	Test Product (n = 12) Hydrocodone TB-047A	Reference Product (n = 12) Hydrocodone 41648
1-hour	Average = 35%. Range = (b) (4)	Average = 23%. Range = (b) (4)
2-hours	Average = 45%. Range = (b) (4)	Average = 34%. Range = (b) (4)
4-hours	Average = 49%. Range = (b) (4)	Average = 48%. Range = (b) (4)
6-hours	Average = 51%. Range = (b) (4)	Average = 55%. Range = (b) (4)
8-hours	Average = 52%. Range = (b) (4)	Average = 58%. Range = (b) (4)
10-hours	Average = 53%. Range = (b) (4)	Average = ~~62~~ 59%. ME 07/06/09 Range = (b) (4)
12-hours	Average = 54%. Range = (b) (4)	Average = 62% Range = (b) (4)

Notebook Ref.: QC0215/28 ; QC0228/75

Transcribed By: (b) (6) Date: 07/10/09

Verified By: (b) (6) Date: 07/10/09

F2 Value (T vs. R): 55.42

6.0 Dissolution Profile Study Test 2 (continue):

Dissolution Profile

Time	Test Product (n = 12) Chlorpheniramine TB-047A	Reference Product (n = 12) Chlorpheniramine 41648
1-hour	Average = 1% Range = (b) (4)	Average = 1% Range = (b) (4)
2-hours	Average = 2% Range = (b) (4)	Average = 2% Range = (b) (4)
4-hours	Average = 2% Range = (b) (4)	Average = 3% Range = (b) (4)
6-hours	Average = 2% Range = (b) (4)	Average = 4% Range = (b) (4)
8-hours	Average = 2% Range = (b) (4)	Average = 4% Range = (b) (4)
10-hours	Average = 2% Range = (b) (4)	Average = 4% Range = (b) (4)
12-hours	Average = 2% Range = (b) (4)	Average = 5% Range = (b) (4)

Notebook Ref.: QC0215/28; QC0228/75

Transcribed By: (b) (6) Date: 07/10/09

Verified By: Date: 07/10/09

F2 Value (T vs. R): 84.57

7.0 Dissolution Profile Study Test 3:

Apparatus: USP Type II (Paddle)
Speed: 50 RPM
Medium: buffer pH 6.8
Volume: 895 mL
Sampling times: 1, 2, 4, 6, 8, 10 and 12 hours

Preparation of pH 6.8 *(Reference: USP – Volumetric Solutions and Reagents: Buffer Solutions)*

1. Preparation of Phosphate solution; Weigh and add 40.83 g of potassium phosphate, monobasic to 1200 mL Water and mix to dissolve. Dilute to 1500 mL with Water.
2. Preparation of 0.2 M Sodium Hydroxide; Mix 200 mL of 1 N NaOH with 1000 mL of Water or mix 20 mL of 10 N NaOH with 1000 mL of Water.
3. Preparation of buffer pH 6.8; Transfer 1500 mL of Phosphate solution to 6-L flask. Add 672 mL of 0.2 M NaOH solution. Dilute to 6 L with DI water. Check pH and adjust to 6.8 (±0.05).

Dissolution Profile

Time	Test Product (n = 12) Hydrocodone TB-047A	Reference Product (n = 12) Hydrocodone 41648
1-hour	Average = 43%. Range = (b) (4)	Average = 26%. Range = (b) (4)
2-hours	Average = 54%. Range = (b) (4)	Average = 42% Range = (b) (4)
4-hours	Average = 60% Range = (b) (4)	Average = 57%. Range = (b) (4)
6-hours	Average = 63%. Range = (b) (4)	Average = 65%. Range = (b) (4)
8-hours	Average = 65%. Range = (b) (4)	Average = 69%. Range = (b) (4)
10-hours	Average = 66%. Range = (b) (4)	Average = ~~72~~ (1) 71%. ME 07/06/09 Range = (b) (4)
12-hours	Average = 67%. Range = (b) (4)	Average = ~~82%~~ 72%. Range = (b) (4)

Notebook Ref.: QC02153/4 ; QC0228/80

Transcribed By: (b) (6) Date: 07/10/09

Verified By: Date: 07/10/09

F2 Value (T vs. R): 53.25

7.0 Dissolution Profile Study Test 3 (continue):

Dissolution Profile				
Time	**Test Product (n = 12)**		**Reference Product (n = 12)**	
	Chlorpheniramine TB-047A		**Chlorpheniramine** 41648	
1-hour	Average = 39 %.	Range = (b) (4)	Average = 25%.	Range = (b) (4)
2-hours	Average = 52%.	Range = (b) (4)	Average = 43%.	Range = (b) (4)
4-hours	Average = 61%.	Range = (b) (4)	Average = 62%. ME 07/06/09	Range = (b) (4)
6-hours	Average = 64%.	Range = (b) (4)	Average = 74%.	Range = (b) (4)
8-hours	Average = 66%.	Range = (b) (4)	Average = 79%	Range = (b) (4)
10-hours	Average = 67%.	Range = (b) (4)	Average = 82%.	Range = (b) (4)
12-hours	Average = 68%.	Range = (b) (4)	Average = 83%.	Range = (b) (4)

Notebook Ref.: QC0215/34 ; QC0228/80

Transcribed By: (b) (6) Date: 07/10/09

Verified By: Date: 07/10/09

F2 Value (T vs. R): **46.08**

Conclusion: The resubmitted individual tablet dissolution data are now legible and confirm the data in the summary tables. The dissolutions profiles of the test product at various pHs are comparable to the dissolution profiles of the reference product (similarity factor F2 values are >50, except for hydrocodone at pH 1.2 and chlorpheniramine at pH 6.8). Since test formulation is different from the reference formulation, f2 factor need not be over 50. Important thing is the test formulation did not show any "dose dumping" at pHs 1.2, 4.5 or 6.8. The response is **acceptable**.

3.6. Recommendations

1. The Division of Bioequivalence finds the fasting BE study (#S08-0404) **acceptable**. Tris Pharma, Inc. conducted the fasting BE study on its Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) comparing it to UCB's Tussionex Pennkinetic®, Eq. 8 mg and 10 mg/5 mL (Lot #41648).

2. The Division of Bioequivalence finds the fed BE study (#S08-0405) **acceptable**. Tris Pharma, Inc. conducted the fasting BE study on its Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) comparing it to UCB's Tussionex Pennkinetic®, Eq. 8 mg and 10 mg/5 mL (Lot #41648).

3. The dissolution testing with a non-FDA-recommended method conducted by Tris Pharma, Inc. on its Chlorpheniramine Polistirex and Hydrocodone Polistirex Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) is **acceptable.**

   The firm should acknowledge the acceptance of dissolution testing as follows:

   Apparatus: 2 (Paddle) at 50 rpm
   Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH not mentioned)
   Temperature: 37 ±0.5°C
   Sampling Time: 1, 3, 6 and 12 hours
   Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

3.7. Comments for Other OGD Disciplines

Discipline	Comment
None	

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet.

Your proposed dissolution method is acceptable. However, based on the dissolution testing results, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5°C
Sampling Time: 1, 3, 6 and 12 hours
Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4. OUTCOME PAGE

CC: ANDA: 91632

5. COMPLETED ASSIGNMENT FOR 091632 ID: 10808

Reviewer: Shrivastava, Surendra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
10808	3/4/2010	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
04/14/2010

SHRINIWAS G NERURKAR
04/14/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
04/15/2010

DIVISION OF BIOEQUIVALENCE REVIEW - AMENDMENT

ANDA No.	091632		
Drug Product Name	Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Oral Suspension		
Strength(s)	Eq. 8 mg and 10 mg/5 mL		
Applicant Name	Tris Pharma, Inc.		
Address	2033 Route 130, Monmouth Junction, NJ 08852		
Applicant's Point of Contact	W. Scott Groner, Dir. Reg. Affairs and Compliance		
Contact's Telephone Number	732-940-0358		
Contact's Fax Number	732-940-0374		
Original Submission Date(s)	July 13, 2009 , March 4, 2010		
Submission Date(s) of Amendment(s) Under Review	**April 26, 2010 (Fax Amendment)** **April 28, 2010 (Telephone Amendment – Requested additional data)**		
Reviewer	S. P. Shrivastava, Ph.D.		
Study Number (s)	S08-0404	S08-0405	
Study Type (s)	Fasting	Fed	
Strength (s)	Eq. 8 mg and 10 mg/5 mL		
Clinical Site	Cetero Research 400 Fountain Lakes Blvd. St. Charles, MO 63301		
Clinical Site Address	See above		
Analytical Site	Cetero Research 10550 Rockley Road Suite 150 Houston, TX 77099		
Analytical Site Address	See above		
Dissolution Testing Site	Tris Pharma, Inc., 2033 Route 130, Monmouth Junction, NJ		
DSI Inspection Status	Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4) which **has not been completed**. Analytical Site Cetero Research, Houston, TX: Routine Inspection for NDA (b) (4) was completed on (b) (4) – Satisfactory.		
OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	N/A		
DSI REPORT RESULT	Pending the inspection of the clinical site (see above)		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
Supporting Document # 1	**DISSOLUTION**	Eq. 8 mg CP and 10 mg HP/5 mL	**INADEQUATE**
Supporting Document # 1	**FASTING STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
ADEQUATE	**FED STUDY**	Eq. 8 mg CP and 10 mg HP/5 mL	**ADEQUATE**
	PERMEABILITY STUDY	N/A	N/A
	SOLUBILITY STUDY	N/A	N/A

1. EXECUTIVE SUMMARY

This application references Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (RLD Tussionex Pennkinetic®, NDA 19111, UCB Inc., Approved 12/31/1987). The firm submitted one fasting and one fed bioequivalence (BE) study on July 13, 2009. According to the earlier review ("full-ANDA" and dissolution testing) the **fasting and fed BE studies were acceptable** and the DBE informed the firm 3 deficiencies that pertained to the dissolution testing [**DARRTS for 91632 SHRIVASTAVA, SURENDRA P 02/04/2010 N/A 02/04/2010 REV-BIOEQ-01(General Review) Original-1**]. The firm satisfactorily responded to the deficiencies (dated March 4, 2010). The DBE concluded that i) the FDA method is not suitable for its product, ii) multimedia dissolution testing is acceptable and iii) the DBE accepted its proposed method but recommended more appropriate specifications as follows:

Time	Hydrocodone	Chlorpheniramine
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

In the current amendment dated April 26 and 28, 2010, the firm has submitted additional dissolution data for 2 new lots, and has requested for revised dissolution specifications as follows:

Time	Hydrocodone	Chlorpheniramine
1 hr	(b) (4)	(b) (4)
3 hr		
6 hr		
12 hr		

Based on the available dissolution data on fresh lots (Biobatch Lot # TB-047A, tested on 4/22-24/2009, 2/24/2010, and new batches, Lot # RD-0286-001 and TB-071A), firm's proposed dissolution specifications are acceptable except for hydrocodone at one-hour time point [to include Biobatch (means 28.6 and 26, Range (b) (4) and (b) (4)], and for chlorpheniramine at 3-hour time point [to include Lot # RD-0286-001 and Biobatch TB-047A (means 65 and 64, Range (b) (4) and (b) (4)]. The firm should acknowledge the acceptance of dissolution specifications as follows:

Time	Hydrocodone	Chlorpheniramine
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Clinical Site Cetero Research, St Charles, MO: Routine Inspection for ANDA 90-740 was ordered on (b) (4) which has not been completed.

Analytical Site Cetero Research, Houston, TX: Routine Inspection for NDA (b) (4) was completed on (b) (4) – Satisfactory.

The application is in**complete (inadequate) pending firm's acknowledgement of the dissolution method and specifications and the results of inspection of the Clinical Site.**

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1.Drug Product Information

Test Product	Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-Release **suspension**, 8 mg/10 mg (equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate) per 5 mL suspension
Reference Product	Tussionex® Pennkinetic® (chlorpheniramine polistirex and hydrocodone polistirex) Extended-Release **Oral Suspension**, equivalent to 8 mg of chlorpheniramine maleate and 10 mg of hydrocodone bitartrate per 5 mL suspension
RLD Manufacturer	UCB Inc.
NDA/ANDA No.	19-111
RLD Approval Date	December 31, 1987
Indication	Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold.
Dosing Regimen	Every 12 hours

3.2.PK/PD Information

See the original Review (DARRTS for 091632 SHRIVASTAVA, SURENDRA P 02/04/2010 N/A 02/04/2010 REV-BIOEQ-01(General Review) Original-1].

Dissolution method and specifications (NDA) [1]

Medium:	Simulated Gastric Fluid (SGF) at 37ºC ± 0.5ºC
Volume:	495 mL
Apparatus:	USP apparatus II (Paddle)
Speed:	50 rpm
FDA-Recommended Specifications:	
• Hydrocodone	1 hour: (b) (4) 3 hours: 8 hours: 24 hour
• Chlorpheniramine	1 hour: (b) (4) 3 hours: 8 hours: 24 hour

3.3.Contents of Submission

Request for revising the dissolution specifications for hydrocodone and chlorpheniramine components in the drug product.

[1] OCPB Review of NDA 19-111, CHOI, YOUNG M 02/01/2002 N/A 02/01/2002 Archive, http://darrts fda.gov:7777/darrts/ViewDocument?documentId=090140af8013dbf7

3.4. Dissolution Method

Source of Method		Firm
Medium		Acidic medium at 0.1 N HCl for 1 hour followed by phosphate buffer until 12 hrs., pH 6.8
Volume (mL)		495 and 895 mL
USP Apparatus type		I1 (Paddle)
Rotation (rpm)		50 rpm
Firm's proposed Specifications	Hydrocodone	1 Hr. (b) (4) 3 Hrs. 6 Hrs. 12 Hrs.
	Chlorpheniramine	1 hr 3 hr 6 hr 12 hr
FDA-recommended specifications (DBE Letter dated, 4/19/2010)	Hydrocodone:	1 hr 3 hr 6 hr 12 hr
	Chlorpheniramine:	1 hr 3 hr 6 hr 12 hr
F2 metric calculated?		Yes
If no, reason why F2 not calculated		N/A
Is method acceptable?		Acceptable
If not then why?		The firm has used its own method. It has also conducted dissolution testing using the FDA-recommended method.

3.5. Deficiencies, Firm's Response and Conclusion

DEFICIENCY-1: *Your proposed dissolution method is acceptable. However, based on the dissolution testing results, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:*

Apparatus: *2 (Paddle) at 50 rpm*
Media: *495 mL 0.1N HCl for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)*
Temperature: *37 ±0.5°C*
Sampling Time: *1, 3, 6 and 12 hours*
Specifications:

TIME	*HYDROCODONE*	*CHLORPHENIRAMINE*
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Firm's Response: The firm conducted dissolution on two additional batches, a duplicate of the original Test Batch ((b) (4) Lot #TB-071A, n=12) and a full scale Batch ((b) (4) Lot # RD-0286-001, n=4). Data for these additional batches are given in Tables 1-4. Data for Biobatch (Lot # TB-047A, n=12) are also presented here for reference (Tables 5-7).

Reviewer's Comments

- The reviewer calculated the Similarity Factor (F2 Value) for hydrocodone and chlorpheniramine. The F2 Values are >50 except for chlopheniramine component in biobatch (tested on 2/24/2010), indicating that the dissolution profiles for both components in the test and reference are more or less similar.

Conclusion: Based on the available dissolution data on fresh lots (Biobatch Lot # TB-047A, tested on 4/22-24/2009, 2/24/2010, and new batches Lot # RD-0286-001 and TB-071A), firm's proposed dissolution specifications are acceptable except for hydrocodone at one-hour time point [to include Biobatch (mean 28.6 and 26, Range (b) (4) and (b) (4) see Tables 5, 7)], and for chlorpheniramine at 3-hour time point [to include Lot # RD-0286-001 and Biobatch TB-047A (means 65 and 64, Range (b) (4) and (b) (4) Tables 4 and 6)]. The firm should acknowledge the acceptance of dissolution method and specifications as follows:

Apparatus:	2 (Paddle) at 50 rpm
Media:	495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature:	37 ±0.5ºC
Sampling Time:	1, 3, 6 and 12 hours
Specifications:	

Time	**Hydrocodone**	**Chlorpheniramine**
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

3.6. Recommendations

1. The dissolution testing with a non-FDA-recommended method conducted by Tris Pharma, Inc. on its Chlorpheniramine Polistirex and Hydrocodone Polistirex

Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) is **incomplete** pending the firm's acknowledgment of the DBE-recommended dissolution specifications as indicated above.

2. The Division of Bioequivalence finds the fasting BE study (#S08-0404) and fed BE study (#S08-0405) acceptable (previously reviewed). Tris Pharma, Inc. conducted the fasting and fed BE studies on its Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Suspension, Eq. 8 mg and 10 mg/5 mL (Lot #TB-047A) comparing it to UCB's Tussionex Pennkinetic®, Eq. 8 mg and 10 mg/5 mL (Lot #41648).

3.7. Comments for Other OGD Disciplines

Discipline	Comment
None	

Table 1. Summary of In Vitro Dissolution Studies – Hydrocodone

Detailed Summary of *In Vitro* Dissolution Studies - **Hydrocodone:**

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate (final pH of 6.8)
	Volume:	5 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications (Hydrocodone)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)** 1	3	6	12	**Study Report Location**
N/A	03/12/10	**Duplicate Test Batch TB-071A** (Date of Mfr: 01/28/10)	Oral Suspension, eq. to 10 and 8mg per 5mL	12	Mean	33	63	70	76	Notebook: QC0616 Page: 006
					Range	(b) (4)				
					%CV	6.4	1.2	0.9	1.8	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	31.8	65.1	72.3	77.6	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	4.92	2.58	1.10	1.02	

T vs. Ref F2 Value = 83.85

Table 2. Summary of In Vitro Dissolution Studies – Chlorpheniramine

Detailed Summary of *In Vitro* Dissolution Studies - **Chlorpheniramine:**

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate (final pH of 6.8)
	Volume:	5 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications (Chlorpheniramine)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)** 1	3	6	12	**Study Report Location**
N/A	03/12/10	**Duplicate Test Batch TB-071A** (Date of Mfr: 01/28/10)	Oral Suspension, eq. to 10 and 8mg per 5mL	12	Mean	1	62	68	75	Notebook: QC0616 Page: 006
					Range	(b) (4)				
					%CV	46.7	1.9	1.1	1.0	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.7	67.0	79.3	85.2	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	6.09	4.68	1.68	1.54	

T vs. Ref F2 Value = 54.64

Table 3. Summary of In Vitro Dissolution Studies – Hydrocodone

Detailed Summary of *In Vitro* Dissolution Studies - **Hydrocodone:**

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate (final pH of 6.8)
	Volume:	5 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications (Hydrocodone)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**				**Study Report Location**
						1	**3**	**6**	**12**	
N/A	03/09/10	**R&D Full Scale Trial Batch RD0286-001** (Date of Mfr: 01/25/10)	Oral Suspension, eq. to 10 and 8mg per 5mL	4	Mean	35	62	67	73	Notebook: RD0246 Page: 184
					Range	(b) (4)				
					%CV	1.4	2.0	1.4	1.1	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	31.8	65.1	72.3	77.6	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	4.92	2.58	1.10	1.02	

Note: No. of Dosage Units tested for Test Lot # RD0286-001 = 4 only; T vs. Ref F2 Value = 68.45

Table 4. Summary of In Vitro Dissolution Studies – Chlorpheniramine

Detailed Summary of *In Vitro* Dissolution Studies - **Chlorpheniramine:**

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate (final pH of 6.8)
	Volume:	5 mL
	Temperature:	37 ºC ± 0.5 ºC
Firm's Proposed Specifications (Chlorpheniramine)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)** 1	3	6	12	**Study Report Location**
N/A	03/09/10	**R&D Full Scale Trial Batch RD0286-001** (Date of Mfr: 01/25/10)	Oral Suspension, eq. to 10 and 8mg per 5mL	4	Mean	0	65	72	78	Notebook: RD0246 Page: 184
					Range	(b) (4)				
					%CV	0.0	3.7	1.3	2.1	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.7	67.0	79.3	85.2	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	6.09	4.68	1.68	1.54	

Note: No. of Dosage Units tested for Test Lot # RD0286-001 = 4 only; T vs. Ref F2 Value = 63.67

Table 5. Summary of In Vitro Dissolution Studies – Hydrocodone

Dissolution Testing Date for Test Product: 4/22-24/2009

Summary of In Vitro Dissolution Studies – Hydrocodone

Dissolution Conditions	**Apparatus:**	USP II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer
	Volume:	5 mL
	Temperature:	37 °C ± 0.5 °C
Firm's Proposed Specifications (Hydrocodone)	1 hour 3 hour 6 hour 12 hour	(b) (4)
Dissolution Testing Site (Name, Address)	Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852	

Study Ref No.	Testing Date	Product ID \ Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 1	3	6	12	Study Report Location
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	28.6	57.6	63.4	68.8	Notebook: QC0214 Page: 085
					Range	(b) (4)				
					%CV	5.54	1.79	1.55	1.52	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	31.8	65.1	72.3	77.6	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	4.92	2.58	1.10	1.02	

F2 Value: 56.14

Table 6. Summary of In Vitro Dissolution Studies - Chlorpheniramine

Dissolution Testing Date for Test Product: 4/22-24/2009

Dissolution Conditions		**Apparatus:**			USP II (Paddle)					
		Speed of Rotation:			50 rpm					
		Medium:			0.1 N HCl, for 1 hr and after sampling add 400mL of Phosphate Buffer					
		Volume:			5 mL					
		Temperature:			37 ºC ± 0.5 ºC					
Firm's Proposed Specifications (Chlorpheniramine)		1 hour (b) (4) 3 hour 6 hour 12 hour								
Dissolution Testing Site (Name, Address)		Tris Pharma, Inc. 2033 Route 130, Monmouth Junction, NJ 08852								
Study Ref No.	**Testing Date**	**Product ID \ Batch No.**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**				**Study Report Location**
						1	**3**	**6**	**12**	
N/A	04/22/09	Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension TB-047A (Date of Mfr: 04/01/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.6	63.6	70.6	75.2	Notebook: QC0214 Page: 085
					Range	(b) (4)				
					%CV	12.3	2.66	1.89	1.57	
N/A	04/24/09	Tussionex® Pennkinetic® 41648 (Expiry Date: 05/09)	Oral Suspension, eq. to 10 and 8mg/5mL	12	Mean	0.7	67.0	79.3	85.2	Notebook: QC0215 Page: 095
					Range	(b) (4)				
					%CV	6.09	4.68	1.68	1.54	

F2 Value: 58.01

Table 7. Hydrocodone and Chlorpheniramine: Test (Firm's Method)

Dissolution Testing Date for Test Product: 2/24/2010

Sampling Time	Test Product			Reference Product		
	Mean	%CV	Range	Mean	%CV	Range
Hydrocodone						
Hours	Lot No. TB 047A			Lot No. 41648		
1	26	5.2	(b) (4)	31.8	4.92	(b) (4)
3	59	2.6		65.1	2.58	
6	68	1.8		72.3	1.10	
12	74	1.8		77.6	1.02	
18	76	1.6		N/A		
24	78	1.8		N/A		
30	80	1.7		N/A		
36	81	1.7		N/A		
f2 metric				64.39		
Chlorpheniramine						
Hours	Lot No. TB 047A			Lot No. 41648		
1	0	0.0	(b) (4)	0.7	6.09	(b) (4)
3	55	3.3		67.0	4.68	
6	62	2.2		79.3	1.68	
12	69	1.8		85.2	1.54	
18	71	1.6		N/A		
24	73	2.4		N/A		
30	77	1.7		N/A		
36	77	2.0		N/A		
f2 metric				43.77		

BIOEQUIVALENCE DEFICIENCIES

ANDA: 91632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Based on the available dissolution data on fresh lots (Biobatch Lot # TB-047A, tested on 4/22-24/2009, 2/24/2010, and new batches Lot # RD-0286-001 and TB-071A), your proposed dissolution specifications are acceptable, except for hydrocodone at one-hour time point, and for chlorpheniramine at 3-hour time point. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5°C
Sampling Time: 1, 3, 6 and 12 hours
Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4. OUTCOME PAGE

CC: ANDA: 091632

5. COMPLETED ASSIGNMENT FOR 091632 ID: 11171

Reviewer: Shrivastava, Surendra **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Chlorpheniramine Polistirex and Hydrocodone Polistirex ER Oral Suspension

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
11171	4/26/2010	Other	Dissolution Amendment	0	0	Edit	Delete
11171	4/28/2010	Other	Dissolution Amendment	1	1	Edit	Delete
				Bean Total:	1		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

SURENDRA P SHRIVASTAVA
05/13/2010

YIH CHAIN HUANG
05/13/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
05/18/2010

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	091632
Drug Product Name	Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension
Strength	10 mg and 8 mg per 5mL
Applicant Name	Tris Pharma
Submission Date	July 13, 2009
Reviewer	Teresa Ramson, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The bioequivalence section of the application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing. The bioequivalence section of the application is acceptable.

I. Completed Assignment for 091632 ID: 11297

Reviewer: Vu, Teresa **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Diss Ackno

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11297	5/27/2010	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

TERESA V RAMSON
05/27/2010

AIDA L SANCHEZ
05/28/2010

DIVISION OF BIOEQUIVALENCE ACCEPTABLE DSI INSPECTION REPORT REVIEW

NDA No.	022439
Drug Product Name	(b) (4) (Hydrocodone, Chlorpheniramine, Pseudoephedrine) Oral Solution
Applicant Name	Cypress Pharmaceutical Inc.
Date of Original Submission	November 06, 2008
Date of Report	May 05, 2010
Project Manager	Diane Nhu, Pharm.D.
Clinical Site	Cetero Research
Clinical Address	400 Fountain Lakes Blvd. St. Charles, MO 63301, USA
DSI Inspection Outcome	Reason for Inspection: Routine Date Requested: (b) (4) Date Completed Outcome: NAI, ADEQUATE

EXECUTIVE SUMMARY

The Division of Scientific Investigations (DSI) inspection report of the **clinical site**, Cetero Research, was received by the Division of Bioequivalence and found acceptable. The site inspection was requested for NDA #22439.

The following applications contained studies conducted at this site:

Clinical Site: Cetero Research
400 Fountain Lakes Blvd.
St. Charles, MO 63301, USA

Given the acceptable inspection of the site, the bioequivalence section of the applications are now acceptable.

ANDA	Firm	Drug Product
078179	Actavis Soutch Atlantic LLC	Zolpidem Tartrate ERT
090427	Apotex, Inc.	Nabumetone Tablets
090606	ENDO Pharmaceuticals Inc.	Mycophenolate Mofetil Tablets
090740	Perrigo R&D Company	Levonorgestrel Tablets
091169	Teva Pharmaceuticals, USA	Eszopiclone Tablets
(b) (4)		
091632	Tris Pharma Inc.	Hydrocodone Polistirex and Chlorpheniramine Polistirex Oral Solution
(b) (4)		

The applications are completed.

COMMENTS:

ANDA	Clinical Site	Analytical Site
078179 090606 (b) (4) 091632 (b) (4)	Cetero Research 400 Fountain Lakes Blvd St. Charles, MO 63301 DSI Inspection History: Parent NDA: 022439, Reason for Inspection: Routine Date Requested: (b) (4) Date Completed: Outcome: NAI, ADEQUATE	(b) (4)
090740		
090427		
(b) (4)		
091169		

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

The Division of Scientific Investigation (DSI) inspection report of the clinical site, Cetero Research, was received by the Division of Bioequivalence on (b) (4) and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

I. Completed Assignment for 022439 ID: 11502

Reviewer: Nhu, Diane **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: DSI Inspection Report Review for NDA 022439, releasing ANDA 090740, (b) (4) 091632, 078179, (b) (4) 091169, 090606, (b) (4) and 090427.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11502	5/1/2010	Other	DSI Inspection Report PMs	1	1
				Bean Total:	1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78179	ORIG-1	ACTAVIS SOUTH ATLANTIC LLC	ZOLPIDEM TARTRATE
ANDA-90427	ORIG-1		NABUMETONE
ANDA-90606	ORIG-1	ENDO PHARMACEUTICALS INC	MYCOPHENOLATE MOFETIL
ANDA-90700	ORIG-1	GLENMARK GENERICS LTD INDIA	VERAPAMIL HYDROCHLORIDE
ANDA-91169	ORIG-1	TEVA PHARMACEUTICALS USA INC	ESZOPICLONE
[redacted] (b) (4)			
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX
[redacted] (b) (4)			

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/s/

DUONG NHU
06/25/2010

BARBARA M DAVIT
06/29/2010

DIVISION OF BIOEQUIVALENCE
DSI REVIEW

ANDA No.	091632
Drug Product Name	Cholorpheniramine Polistirex and Hydrocodone Polistirex ER Oral Suspension
Strength	Eq. 8 mg and 10 mg/5 mL
Applicant Name	Tris Pharma, Inc
Date of Original Submission	July 13, 2009, March 4, 2010
Reviewer	Alpita Popat, PharmD, MBA Cetero Research
Clinical Site Name/Address	400 Fountain Lakes Blvd St. Charles, MO 63301
	Date Requested: (b) (4) Date Completed Outcome: VAI

EXECUTIVE SUMMARY

The application was pending a routine Division of Scientific Investigation (DSI) inspection for clinical site linked to ANDA 090740. The DSI inspection report for the parent ANDA was received by the Division of Bioequivalence on (b) (4) The outcome was found VAI and DBE agrees with the DSI findings and found the report acceptable.

The clinical and analytical site for ANDA 091632 is not pending the outcome of DSI

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

This application was pending a routine Division of Scientific Investigation (DSI) inspection for clinical site linked to ANDA 090740. The DSI inspection report of clinical sites was received by the Division of Bioequivalence on (b) (4) for ANDA 090740 and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

I. Completed Assignment for 091632 ID: 12585

Back to Main Menu

Reviewer: Popat, Alpita **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: DSI Report for Cholorpheniramine Polistirex and Hydrocodone Polistirex ER Oral Suspension

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Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
12585	11/12/2010	Other	DSI Inspection Report PMs	1	1	Edit	Delete
				Bean Total:	1		

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/s/

ALPITA POPAT
11/12/2010

AIDA L SANCHEZ
11/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091632

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Potential First to File
No Blocking Patents

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

July 13, 2009

Mr. Gary Buehler, Director OGD
Office of Generic Drugs
CDER/FDA (HFD-600)
Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632, Pre-Assigned ANDA Original Application
Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Buehler:

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an original abbreviated new drug application, ANDA 091632 (Pre-Assigned ANDA Original Application), seeking approval to market Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL, that is therapeutically equivalent to the reference product Tussionex® Pennkinetic® NDA No. 019111, manufactured by UCB, Inc.

There are no unexpired patents or exclusivities for this product as listed in the Orange Book. This ANDA contains a "Paragraph II Certification". Fasted and Fed *in vivo* bioequivalence studies were performed and are included in this submission along with all Chemistry and Manufacturing Controls for this product necessary for the approval of this application. **As this application is for a potential first to file product for which there are no blocking patents or exclusivity protections on the reference listed drug, Tris requests an expedited review as provided for by the Generic Initiative for Value and Efficiency (GIVE).**

This eCTD is approximately 400 megabytes saved to a DVD disk. Symantec AntiVirus software, version 10.0.2.2000, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4), eCentral, version 2.03.

Please forward any written communications regarding this ANDA original application to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-632

Tris Pharma, Inc.
Attention: W. Scott Groner
2033 Route 130
Monmouth Junction, NJ 08502

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 14, 2009, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-release Oral Suspension, EQ 8 mg Maleate and EQ 10 mg Bitartrate per 5 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The concentration of the inactive ingredient (Sodium Ascorbate) in your proposed drug product (b) (4) of this inactive ingredient previously approved by the Agency in an orally administered drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide additional justification to demonstrate safety, such as pharmacology/toxicology data.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, please provide:

1.) Composition breakdown of (b) (4) Sodium Polystyrene Sulfonate (b) (4)
2.) Revise cGMP for (b) (4) to cite appropriate CFR.
3.) Revise cGMP for (b) (4) to cite appropriate CFR.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Lisa Tan
Project Manager
(240) 276-8420

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FELECIA TAN
08/07/2009

MARTIN H Shimer
08/13/2009
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
** **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 91-632 **FIRM NAME**: TRIS PHARMA
(EXPEDITED REQUEST REVIEW)

PIV: NA **Electronic or Paper Submission:** ECTD FORMAT
(ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: CHLORPHENIRAMINE POLISTIREX AND HYDROCODONE POLISTIREX

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DOSAGE FORM: EXTENDED RELEASE ORAL SUSPENSION, 10 MG AND 8 MG PER 5 ML

Random Queue: 4

Chem Team Leader:Liu, Shing Hou Chem PM: Leign Ann Bradford
Labeling Reviewer: BurhanNour Bio PM: Steven Mazzella
Add FYI Assignment – Aida L. Sanchez

Letter Date: JULY 13, 2009 **Received Date**: JULY 14, 2009

Comments: EC- 2 YES **On Cards:** YES
Therapeutic Code: 6010405 ANTITUSSIVE /ANTIHISTAMINE

Archival copy: ECTD FORMAT **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Lisa Tan	**Recommendation:**
Date 8/4/2009	☐ **FILE** ☒ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Contact Info: W. Scott Groner 732.940.0358 reg.affairs@trispharma.com

Request:

1.) **Revise cGMP for** (b) (4) **to cite appropriate CFR.**
2.) **Revise cGMP for** (b) (4) **to cite appropriate CFR.**
3.) **Composition breakdown of** (b) (4)

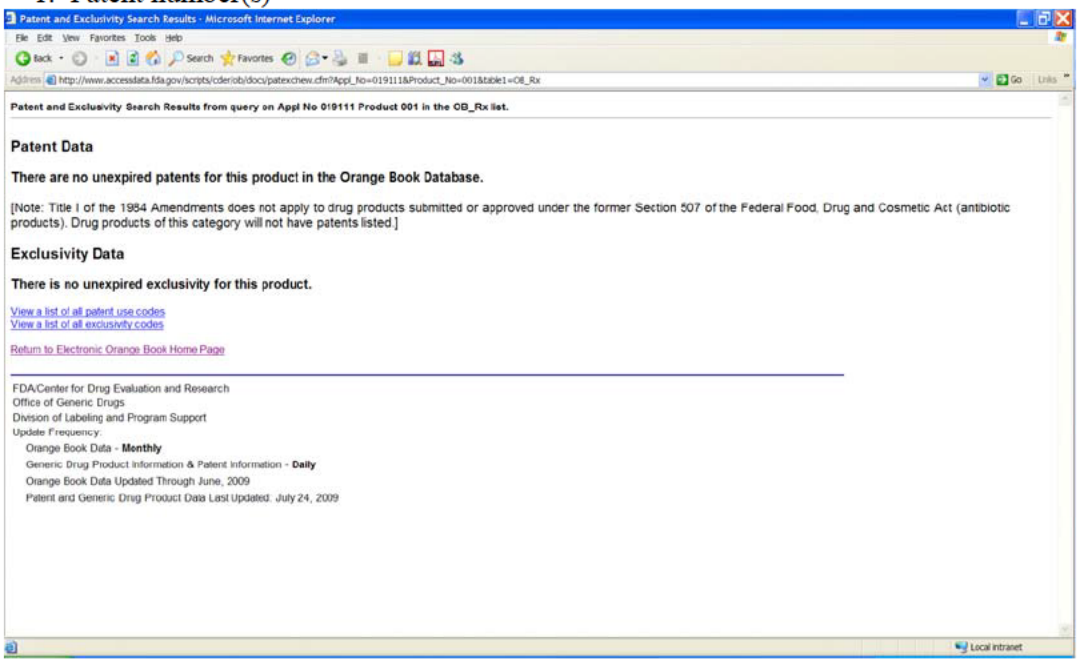
Notes:
8/4/2009:
Spoke with Shing Liu regarding high fructose corn syrup and sodium ascorbate.
With regards to high fructose corn syrup, (b) (4)

With regards to the sodium ascorbate, (b) (4) **Please also reference control correspondence, 07-1145 dated 2/14/2008 for additional material regarding this inactive. A copy of the control is at the end of the checklist.**

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JULY 13, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES** Option B	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒

1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s)  Patent and Exclusivity Search Results - Microsoft Internet Explorer File Edit View Favorites Tools Help http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexchew.cfm?Appl_No=019111&Product_No=001&table1=OB_Rx **Patent and Exclusivity Search Results from query on Appl No 019111 Product 001 in the OB_Rx list.** **Patent Data** **There are no unexpired patents for this product in the Orange Book Database.** [Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.] **Exclusivity Data** **There is no unexpired exclusivity for this product.** View a list of all patent use codes View a list of all exclusivity codes Return to Electronic Orange Book Home Page FDA/Center for Drug Evaluation and Research Office of Generic Drugs Division of Labeling and Program Support Update Frequency: Orange Book Data - **Monthly** Generic Drug Product Information & Patent Information - **Daily** Orange Book Data Updated Through June, 2009 Patent and Generic Drug Product Data Last Updated: July 24, 2009 Local intranet 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? n/a b. Expiration of Pediatric Exclusivity? n/a 4. Exclusivity Statement: YES no unexpired exclusivity	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient hydrocodone= (b) (4) chlorpheniramine= (b) (4) b. Type III DMF authorization letter(s) for container closure (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) n/a	☒

1.12.11	**Basis for Submission** NDA# : 19-111 Ref Listed Drug: TUSSIONEX PENNKINETIC Firm: UCB INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use same 2. Active ingredients same 3. Inactive ingredients	☒

	Tris Product	Reference Product [1]
Conditions of use	Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.	Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.
Drug Substance	Hydrocodone Bitartrate USP [2] Chlorpheniramine Maleate USP [2]	Hydrocodone Polistirex Chlorpheniramine Polistirex
Inactive Ingredients	Purified Water USP Polyvinyl Acetate (b) (4) Triacetin USP Sodium Metabisulfite NF Polysorbate 80 NF Propylene Glycol USP Methylparaben NF Propylparaben NF Xanthan Gum NF Ascorbic Acid USP Sodium Ascorbate USP High Fructose Corn Syrup Sucrose NF D&C Yellow No. 10 (b) (4) Food Starch Modified) (b) (4) Flavor (b) (4) (b) (4)	Purified Water Ethylcellulose Vegetable Oil Polysorbate 80 Propylene Glycol Polyethylene Glycol 3350 Methylparaben Propylparaben Xanthan Gum Ascorbic acid High Fructose Corn Syrup Sucrose D&C Yellow No. 10 FD&C Yellow No. 6 Pregelatinized Starch Flavor

4. Route of administration same
5. Dosage Form same
6. Strength same

1.12.14	**Environmental Impact Analysis Statement** YES 21cfr25.31	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☒

1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) yes **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained yes **1.14.1.3** 1 package insert (content of labeling) submitted electronically yes ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained yes **1.14.3.3** 1 RLD label and 1 RLD container label yes	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** yes **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** yes **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** yes **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary yes Table 4. Bioanalytical Method Validation yes Table 6. Formulation Data yes **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies yes Table 3. Statistical Summary of the Comparative BA Data yes **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies yes	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒

3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) Hydrocodone: Tris Pharma Inc Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension **2.3.S.2 Manufacture:** **Who manufactures the drug substance?** Manufacturer: (b) (4) Supplier: (b) (4) Chlorpheniramine: **2.3.S.2 Manufacture:** **Who manufactures the drug substance?** Manufacturer: (b) (4) Supplier: (b) (4) 2. Function or Responsibility yes 3. Type II DMF number for API hydrocodone= (b) (4) chlorpheniramine= (b) (4) 4. CFN or FEI numbers hydrocodone= (b) (4) chlorpheniraminde= (b) (4)	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) yes **3.2.S.4.2 Analytical Procedures** yes **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples yes 2. Samples-Statement of Availability and Identification of: a. Drug Substance yes b. Same lot number(s) hydrocondone=08LW662 chlorpheniramine=5Y050S **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) yes 2. Applicant certificate of analysis yes **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials** submitted	☒
3.2.S.6	**Container Closure Systems** refer to dmf	☒
3.2.S.7	**Stability** refer to dmf	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition yes 2. Inactive ingredients and amounts are appropriate per IIG justified per IIG	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report yes	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **Who manufactures the drug product?** Tris Pharma, Inc. 2033 Route 130 Monmouth Junction, NJ 08852 2. CGMP Certification: YES 3. Function or Responsibility yes 4. CFN or FEI numbers 3004712471 **3.2.P.3.2 Batch Formula** yes **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization n/a 4. Reprocessing Statement 21cfr211.115 **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation n/a 2. Filter validation (if aseptic fill) n/a	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified yes **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) yes 2. Suppliers' COA (specifications and test results) yes **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA yes	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

<table>
<tr><td>3.2.P.5</td><td>Controls of Drug Product
3.2.P.5.1 Specification(s) yes
3.2.P.5.2 Analytical Procedures yes
3.2.P.5.3 Validation of Analytical Procedures
Samples - Statement of Availability and Identification of:
1. Finished Dosage Form yes
2. Same lot numbers TB-047A
3.2.P.5.4 Batch Analysis
Certificate of Analysis for Finished Dosage Form yes
3.2.P.5.5 Characterization of Impurities
3.2.P.5.6 Justification of Specifications</td><td>☒</td></tr>
<tr><td>3.2.P.7</td><td>Container Closure System
1. Summary of Container/Closure System (if new resin, provide data) yes
2. Components Specification and Test Data yes
3. Packaging Configuration and Sizes
<table><tr><th>Material</th><th>Supplier</th><th>Manufacturer</th></tr><tr><td>Container, 16 oz. (b) (4) Clear Glass (b) (4) Round Container (b) (4)

Closure, 28mm (b) (4) White, (b) (4) Smooth Top Closure (b) (4)</td><td colspan="2">(b) (4)</td></tr></table>4. Container/Closure Testing yes
5. Source of supply and suppliers address yes</td><td>☒</td></tr>
<tr><td>3.2.P.8</td><td>3.2.P.8.1 Stability (Finished Dosage Form)
1. Stability Protocol submitted yes
2. Expiration Dating Period 24 month exp
3.2.P.8.2 Post-approval Stability and Conclusion
Post Approval Stability Protocol and Commitments yes
3.2.P.8.3 Stability Data
1. 3 month accelerated stability data yes
2. Batch numbers on stability records the same as the test batch yes:TB-047A</td><td>☒</td></tr>
</table>

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NA** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation yes Theoretical Yield see below Actual Yield see below Packaged Yield see below **3.2.R.1.P.2 Information on Components** yes **3.2.R.2.P Comparability Protocols** n/a **3.2.R.3.P Methods Validation Package** NA Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type:** (Continue with the appropriate study type box below)	☐

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) ☒

Statistical Summary of the Comparative Bioavailability Data – Hydrocodone

Hydrocodone 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=30[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	158.11	160.46	98.54	(95.00, 102.20)
AUC_{0-inf}	161.38	163.45	98.73	(95.36, 102.23)
C_{max}	14.56	15.05	96.73	(93.12, 100.48)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	184.85	188.84	97.89	(93.61, 102.36)
AUC_{0-inf}	187.76	191.65	97.97	(93.74, 102.40)
C_{max}	14.85	14.85	99.95	(96.06, 104.00)

Statistical Summary of the Comparative Bioavailability Data – Chlorpheniramine

Chlorpheniramine 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=29[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	391.89	409.19	95.77	(91.25, 100.52)
AUC_{0-inf}	431.33	452.78	95.26	(90.41, 100.37)
C_{max}	12.21	12.99	93.99	(88.62, 99.69)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	401.31	399.80	100.38	(95.24, 105.79)
AUC_{0-inf}	435.25	430.18	101.18	(96.25, 106.35)
C_{max}	11.55	11.62	99.45	(93.41, 105.88)

2. Summary Bioequivalence tables:
   Table 10. Study Information yes
   Table 12. Dropout Information yes
   Table 13. Protocol Deviations yes

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 11. Product Information yes
   Table 16. Composition of Meal Used in Fed Bioequivalence Study yes

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   Table 9. Reanalysis of Study Samples yes
   Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses yes
   Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples yes

5.3.7

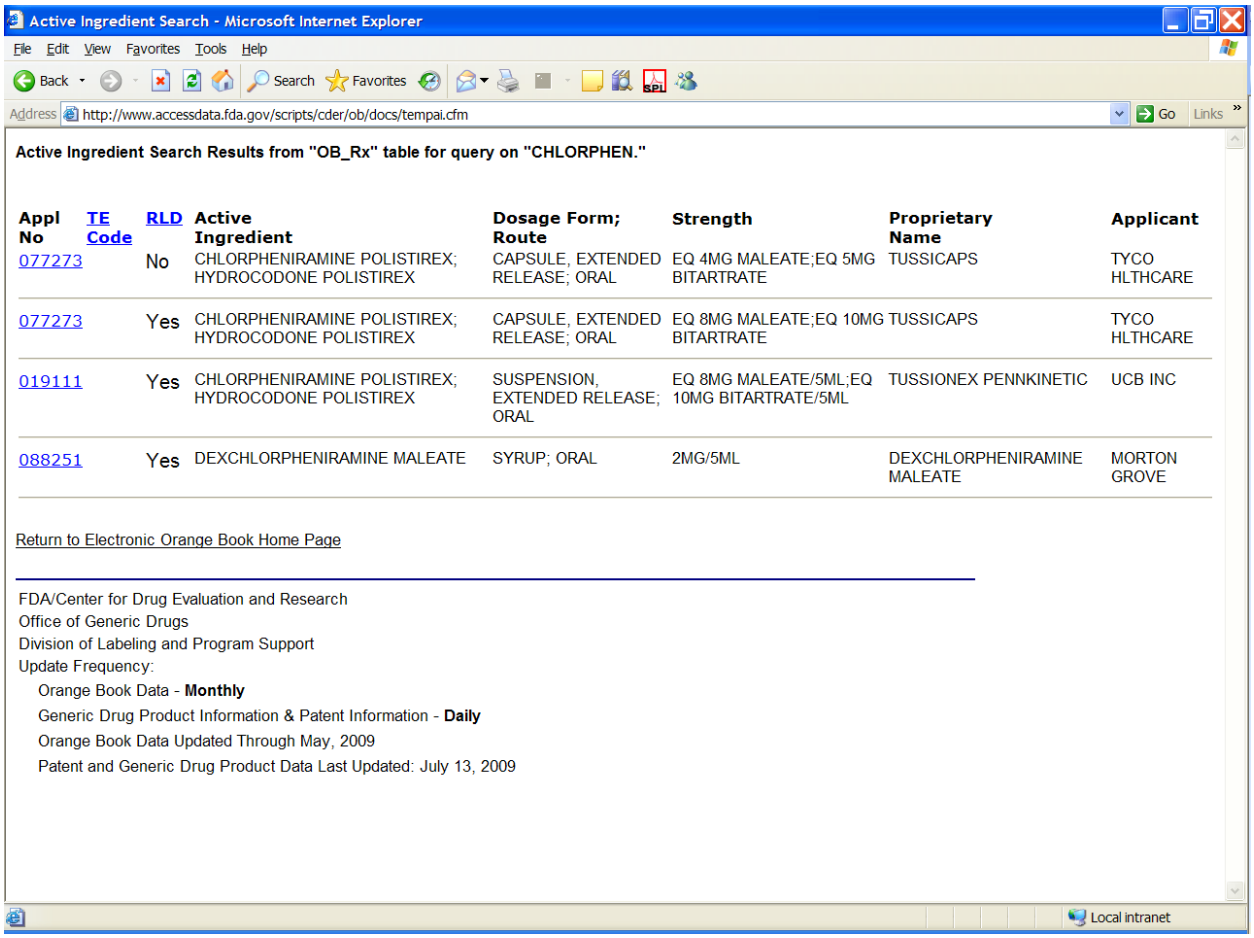
Case Report Forms and Individual Patient Listing yes

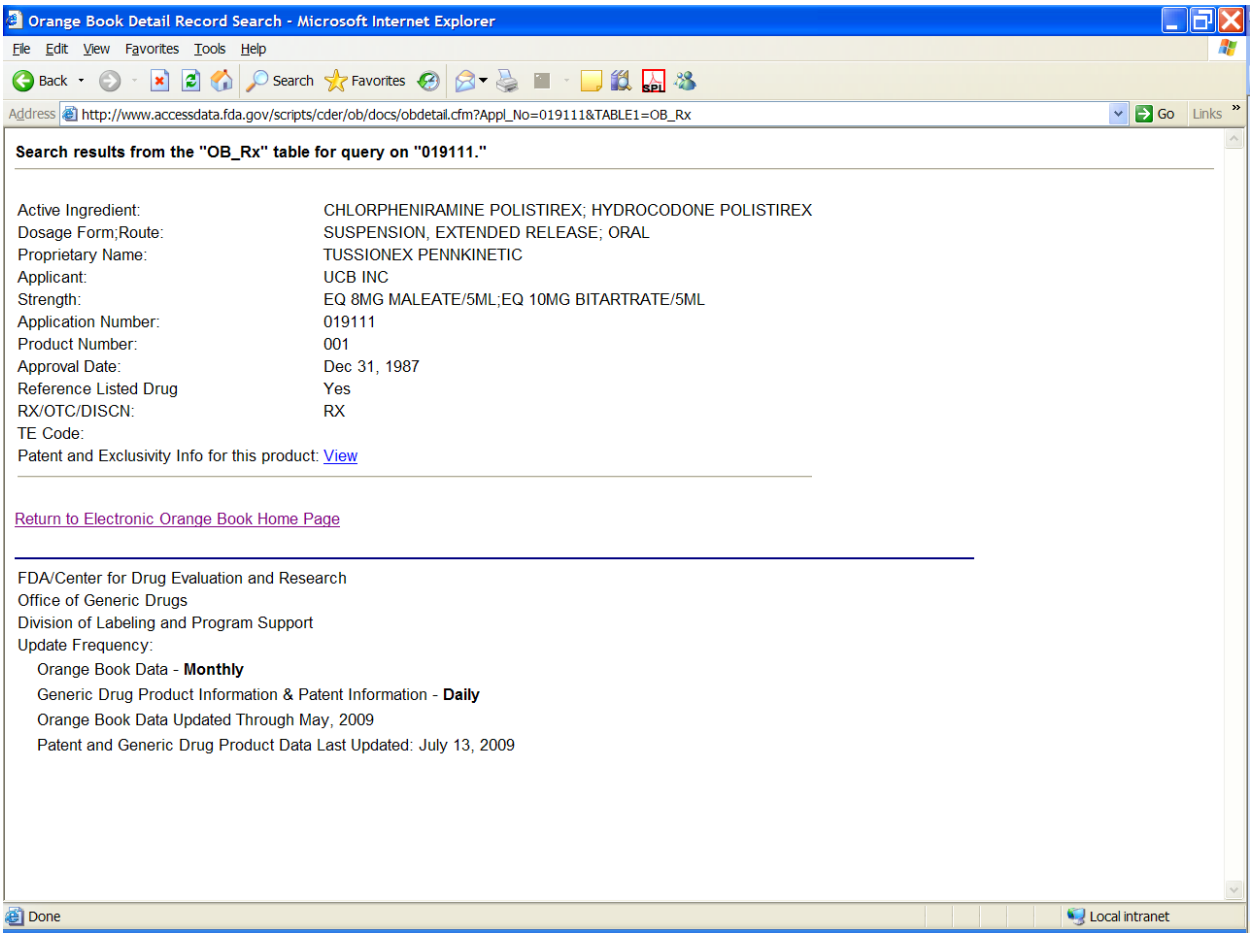
5.4	**Literature References**	☐

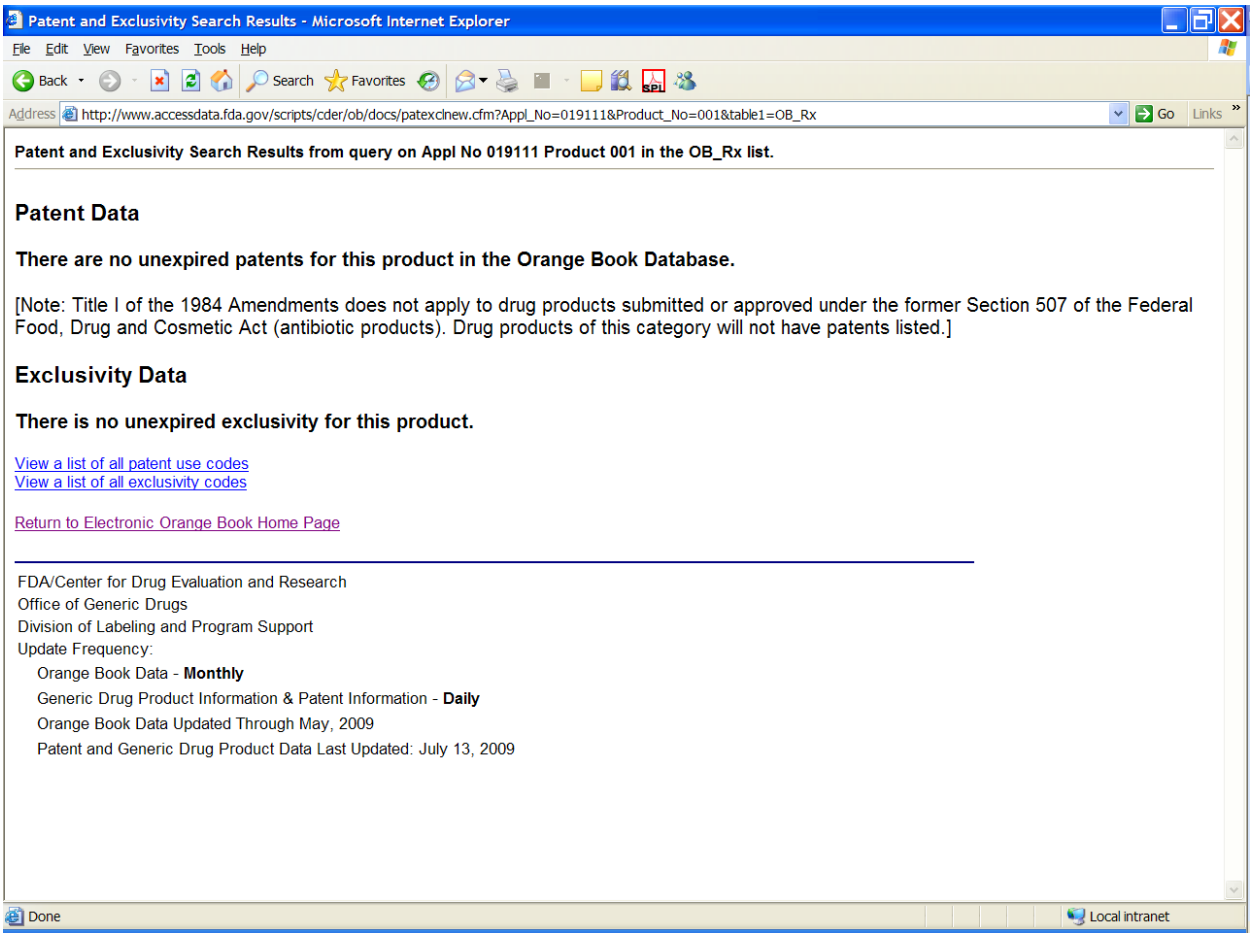
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 10MG AND 8 MG PER 5 ML 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)yes 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
Active Ingredient Search Results from "OB_Rx" table for query on "CHLORPHEN."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
077273 | | No | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | CAPSULE, EXTENDED RELEASE; ORAL | EQ 4MG MALEATE;EQ 5MG BITARTRATE | TUSSICAPS | TYCO HLTHCARE
077273 | | Yes | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | CAPSULE, EXTENDED RELEASE; ORAL | EQ 8MG MALEATE;EQ 10MG BITARTRATE | TUSSICAPS | TYCO HLTHCARE
019111 | | Yes | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | SUSPENSION, EXTENDED RELEASE; ORAL | EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML | TUSSIONEX PENNKINETIC | UCB INC
088251 | | Yes | DEXCHLORPHENIRAMINE MALEATE | SYRUP; ORAL | 2MG/5ML | DEXCHLORPHENIRAMINE MALEATE | MORTON GROVE
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 13, 2009
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=019111&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "019111."
Active Ingredient: CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX
Dosage Form;Route: SUSPENSION, EXTENDED RELEASE; ORAL
Proprietary Name: TUSSIONEX PENNKINETIC
Applicant: UCB INC
Strength: EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML
Application Number: 019111
Product Number: 001
Approval Date: Dec 31, 1987
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 13, 2009
Done
Local intranet



OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #91-632 **APPLICATION: TRIS PHARMA**
DATE OF SUBMISSION: 7/13/2009

DRUG: Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-Release Oral Suspension,10mg and 8mg Per 5 mL

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☐ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: **SELECT TEAM # 4 Leigh Ann Bradford**
a) When expedited review is denied, notify the applicant by telephone

DATE

ENTER FORM INTO DFS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FELECIA TAN
08/07/2009

MARTIN H Shimer
08/13/2009

Potential First to File
No Blocking Patents

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

August 26, 2009

Ms. Felecia Tan, Project Manager
Office of Generic Drugs
CDER/FDA (HFD-600)
Document Room E-150
7500 Standish Place
Rockville, MD 20855
(240) 276-8420

Reference: ANDA 091632 Amendment, Sequence 0001
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Tan:

Reference is made to a Refusal to File communication received on August 13, 2009 from the Regulatory Project Manager for ANDA 091632 Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an amendment to the abbreviated new drug application, ANDA 091632, Sequence 0001, which includes complete responses to all of the deficiencies. Full details of these deficiencies and the Tris responses are found in the attachment to this cover letter. **As this application is for a potential first to file product for which there are no blocking patents or exclusivity protections on the reference listed drug, Tris requests an expedited review as provided for by the Generic Initiative for Value and Efficiency (GIVE).**

This eCTD is approximately 700 megabytes saved to a DVD disk. Symantec AntiVirus software, version 10.0.2.2000, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 2.03.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Tris Pharma Inc.
Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension

Deficiency 1

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> ***The concentration of the inactive ingredient (Sodium Ascorbate) in your proposed drug product*** (b) (4) ***of this inactive ingredient previously approved by the Agency in an orally administered drug product. Therefore, the proposed product cannot be approved as an ANDA [21 CFR 314.127(a)(8)(ii)]. Please provide additional justification to demonstrate safety, such as pharmacology/toxicology data.***

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Response 1

(b) (4)

Deficiency 2

In addition, please provide the composition breakdown of (b) (4) (b) (4)

Response 2

(b) (4)

Deficiency 3

In addition, please provide a revised cGMP for (b) (4) to cite appropriate CFR.

Response 3

A revised cGMP statement from (b) (4) citing 21 CFR 210 and 211 has been provided, refer to Module 3.2.S.2.1.

Deficiency 4

In addition, please provide a revised cGMP for (b) (4) to cite appropriate CFR.

Response 4

A revised cGMP statement from (b) (4) citing 21 CFR 210 and 211 has been provided, refer to Module 3.2.S.2.1.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2009-0343	
TO *(Division/Office)* DPAP - HFD-570 Thru: Leah Ripper, ODEII - HFD 102			FROM: Felecia Tan	
DATE: 8/27/2009	IND NO.	ANDA NO. 91-632	TYPE OF DOCUMENT Amendment	DATE OF DOCUMENT 8/26/2009,
NAME OF DRUG Sodium Ascorbate		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG antitussive/antihistimine	DESIRED COMPLETION DATE 10/26/2009
NAME OF FIRM Tris Pharma Inc.				

REASON FOR REQUEST

I. GENERAL

- ✆ NEW PROTOCOL
- ✆ PROGRESS REPORT
- ✆ NEW CORRESPONDENCE
- ✆ DRUG ADVERTISING
- ✆ ADVERSE REACTION REPORT
- ✆ MANUFACTURING CHANGE/ADDITION
- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
- ✆ PAPER NDA
- ✆ CONTROL SUPPLEMENT
- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV.DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- _SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL PRECLINICAL

COMMENTS

OGD is requesting a pharm/tox review of sodium ascorbate,In OGD database, the MDD level for this inactive is (b) (4) The firm is stating the excipient is ultimatlev ascorbic acid (vit c) and has provide justification as such. Please review their submission and provide comments to if their proposed level of (b) (4) is safe for human use.Please cc Theresa Liu, HFD-617 (Theresa.Liu@fda.hhs.gov) on the review when it is being checked into DFS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 91632	ORIG 1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX
ANDA 91632	ORIG 1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX
ANDA 91632	ORIG 1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FELECIA TAN
08/28/2009

THERESA C LIU
08/28/2009

RTR RESPONSE

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www.fda.gov/cder/regulatory/ersr/ectd htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
** **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 91-632 **FIRM NAME**: TRIS PHARMA
(EXPEDITED REQUEST REVIEW)

PIV: NA **Electronic or Paper Submission:** ECTD FORMAT
(ELECTRONIC DATA)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: CHLORPHENIRAMINE POLISTIREX AND HYDROCODONE POLISTIREX

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	
☐ **BST**	☒ **BDI**	

DOSAGE FORM: EXTENDED RELEASE ORAL SUSPENSION, 10 MG AND 8 MG PER 5 ML

Random Queue: 4

Chem Team Leader:Liu, Shing Hou Chem PM: Leign Ann Bradford
Labeling Reviewer: BurhanNour Bio PM: Steven Mazzella
Add FYI Assignment – Aida L. Sanchez

Letter Date: JULY 13, 2009 **Received Date**: AUGUST 26, 2009

Comments: EC- 2 YES **On Cards:** YES
Therapeutic Code: 6010405 ANTITUSSIVE /ANTIHISTAMINE

Archival copy: ECTD FORMAT **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Lisa Tan Date 8/27/2009	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

Contact Info: W. Scott Groner 732.940.0358 reg.affairs@trispharma.com

8/27/2009: RESPONSE TO RTR:
FIRM HAS SUBMITTED A RESPONSE IN WHICH THEY PROVIDED PHARM/TOX DATA FOR THE SODIUM ASCORBATE. THE PHARM/TOX DATA HAS BEEN SENT OUT ON CONSULT TO OND. ALL ITEMS HAVE BEEN ADDRESSED FROM THE RTR AND THIS SUBMSSION RESPONSE IS ACCEPTABLE FOR FILING.

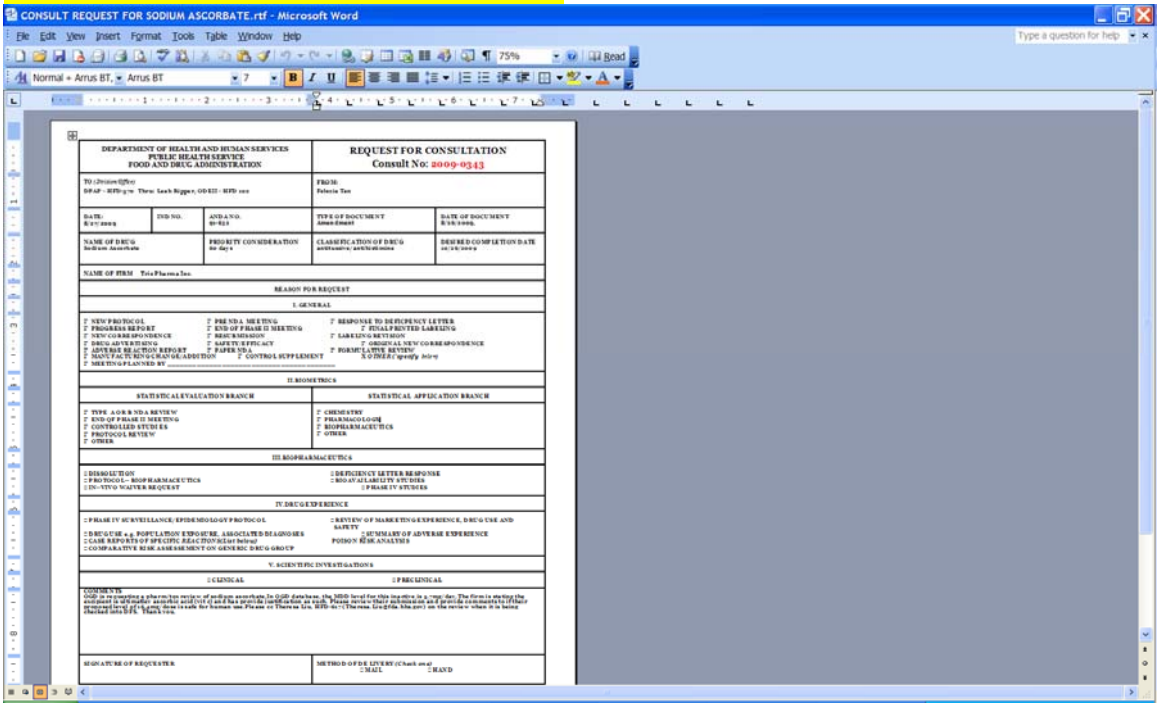
RTR:
Request:

1.) **Revise cGMP for** (b) (4) **to cite appropriate CFR.**
2.) **Revise cGMP for** (b) (4) **to cite appropriate CFR.**
3.) **Composition breakdown of** (b) (4)

Notes:
8/4/2009:
Spoke with Shing Liu regarding high fructose corn syrup and sodium ascorbate.
With regards to high fructose corn syrup (b) (4)

With regards to the sodium ascorbate, Shing Liu said (b) (4) (b) (4) **Please also reference control correspondence, 07-1145 dated 2/14/2008 for additional material regarding this inactive. A copy of the control is at the end of the checklist.**

CONSULT FOR SODIUM ASCORBATE:


CONSULT REQUEST FOR SODIUM ASCORBATE.rtf - Microsoft Word

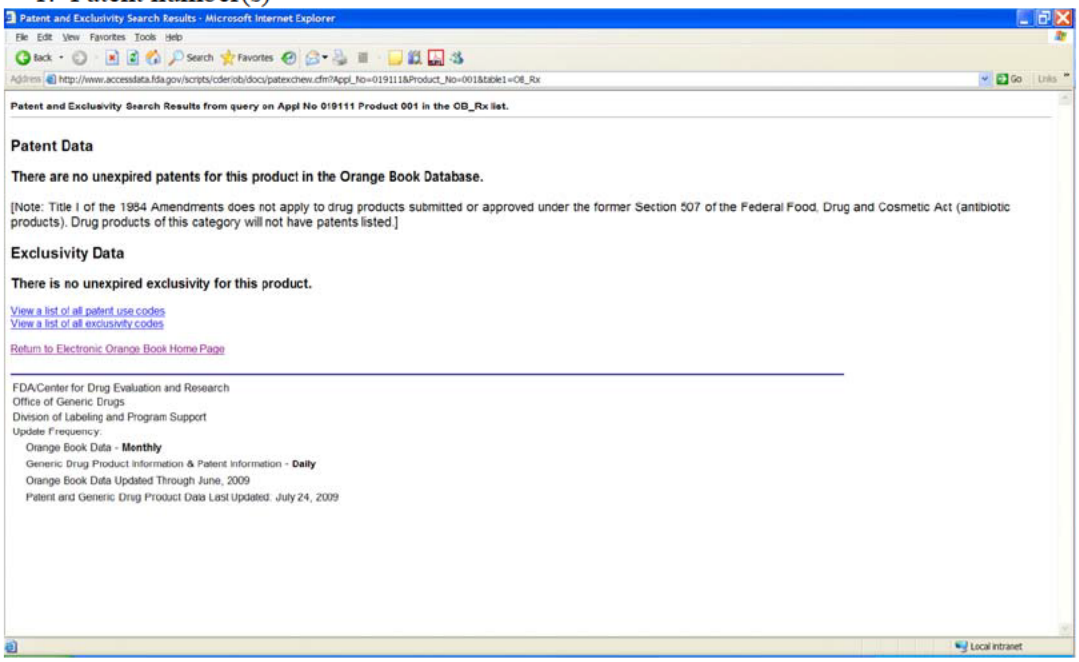
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION
Consult No: 2009-0343

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JULY 13, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES** Option B	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** NA **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒

1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s)  Patent and Exclusivity Search Results - Microsoft Internet Explorer File Edit View Favorites Tools Help http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexchew.cfm?Appl_No=019111&Product_No=001&table1=OB_Rx **Patent and Exclusivity Search Results from query on Appl No 019111 Product 001 in the OB_Rx list.** **Patent Data** **There are no unexpired patents for this product in the Orange Book Database.** [Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.] **Exclusivity Data** **There is no unexpired exclusivity for this product.** View a list of all patent use codes View a list of all exclusivity codes Return to Electronic Orange Book Home Page FDA/Center for Drug Evaluation and Research Office of Generic Drugs Division of Labeling and Program Support Update Frequency: Orange Book Data - **Monthly** Generic Drug Product Information & Patent Information - **Daily** Orange Book Data Updated Through June, 2009 Patent and Generic Drug Product Data Last Updated: July 24, 2009 Local intranet 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☒ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? n/a b. Expiration of Pediatric Exclusivity? n/a 4. Exclusivity Statement: YES no unexpired exclusivity	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient hydrocodone (b) (4) chlorpheniramine= (b) (4) b. Type III DMF authorization letter(s) for container closure (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) n/a	☒
1.12.11	**Basis for Submission** NDA# : 19-111 Ref Listed Drug: TUSSIONEX PENNKINETIC Firm: UCB INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>1.12.12</td><td>Comparison between Generic Drug and RLD-505(j)(2)(A)
1. Conditions of use same
2. Active ingredients same
3. Inactive ingredients
<table><tr><th></th><th>Tris Product</th><th>Reference Product [1]</th></tr><tr><td>Conditions of use</td><td>Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.</td><td>Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.</td></tr><tr><td>Drug Substance</td><td>Hydrocodone Bitartrate USP [2]
Chlorpheniramine Maleate USP [2]</td><td>Hydrocodone Polistirex
Chlorpheniramine Polistirex</td></tr><tr><td>Inactive Ingredients</td><td>Purified Water USP
Polyvinyl Acetate (b) (4)
Triacetin USP
Sodium Metabisulfite NF
Polysorbate 80 NF
Propylene Glycol USP
Methylparaben NF
Propylparaben NF
Xanthan Gum NF
Ascorbic Acid USP
Sodium Ascorbate USP
High Fructose Corn Syrup
Sucrose NF
D&C Yellow No. 10
(b) (4) Food Starch Modified)
(b) (4) Flavor (b) (4)
(b) (4)</td><td>Purified Water
Ethylcellulose
Vegetable Oil
Polysorbate 80
Propylene Glycol
Polyethylene Glycol 3350
Methylparaben
Propylparaben
Xanthan Gum
Ascorbic acid
High Fructose Corn Syrup
Sucrose
D&C Yellow No. 10
FD&C Yellow No. 6
Pregelatinized Starch
Flavor</td></tr></table>4. Route of administration same
5. Dosage Form same
6. Strength same</td><td>☒</td></tr>
<tr><td>1.12.14</td><td>Environmental Impact Analysis Statement YES 21cfr25.31</td><td>☒</td></tr>
<tr><td>1.12.15</td><td>Request for Waiver
Request for Waiver of In-Vivo BA/BE Study(ies): NA</td><td>☒</td></tr>
<tr><td>1.14.1</td><td>Draft Labeling (Mult Copies N/A for E-Submissions)
1.14.1.1 4 copies of draft (each strength and container) yes
1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained yes
1.14.1.3 1 package insert (content of labeling) submitted electronically yes
***Was a proprietary name request submitted? no
(If yes, send email to Labeling Reviewer indicating such.)</td><td>☒</td></tr>
<tr><td>1.14.3</td><td>Listed Drug Labeling
1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained yes
1.14.3.3 1 RLD label and 1 RLD container label yes</td><td>☒</td></tr>
</table>

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** yes **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** yes **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** yes **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** yes **Word Processed e.g., MS Word** yes **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary yes Table 4. Bioanalytical Method Validation yes Table 6. Formulation Data yes **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution yes **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies yes Table 3. Statistical Summary of the Comparative BA Data yes **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study yes **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies yes	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information SUBMITTED** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) Hydrocodone: Tris Pharma Inc Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension **2.3.S.2 Manufacture:** **Who manufactures the drug substance?** Manufacturer: (b) (4) Supplier: (b) (4) Chlorpheniramine: **2.3.S.2 Manufacture:** **Who manufactures the drug substance?** Manufacturer: (b) (4) Supplier: (b) (4) 2. Function or Responsibility yes 3. Type II DMF number for API hydrocodone= (b) (4) chlorpheniramine= (b) (4) 4. CFN or FEI numbers hydrocodone= (b) (4) chlorpheniraminde= (b) (4)	☒

3.2.S.3	**Characterization SUBMITTED**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) yes **3.2.S.4.2 Analytical Procedures** yes **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples yes 2. Samples-Statement of Availability and Identification of: a. Drug Substance yes b. Same lot number(s) hydrocondone=08LW662 chlorpheniramine=5Y050S **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) yes 2. Applicant certificate of analysis yes **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials** submitted	☒
3.2.S.6	**Container Closure Systems** refer to dmf	☒
3.2.S.7	**Stability** refer to dmf	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition yes 2. Inactive ingredients and amounts are appropriate per IIG justified per IIG	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report yes	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) **Who manufactures the drug product?** Tris Pharma, Inc. 2033 Route 130 Monmouth Junction, NJ 08852 2. CGMP Certification: YES 3. Function or Responsibility yes 4. CFN or FEI numbers 3004712471 **3.2.P.3.2 Batch Formula** yes **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization n/a 4. Reprocessing Statement 21cfr211.115 **3.2.P.3.4 Controls of Critical Steps and Intermediates** **3.2.P.3.5 Process Validation and/or Evaluation** 1. Microbiological sterilization validation n/a 2. Filter validation (if aseptic fill) n/a	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified yes **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) yes 2. Suppliers' COA (specifications and test results) yes **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA yes	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

<table>
<tr><td>3.2.P.5</td><td>Controls of Drug Product
3.2.P.5.1 Specification(s) yes
3.2.P.5.2 Analytical Procedures yes
3.2.P.5.3 Validation of Analytical Procedures
Samples - Statement of Availability and Identification of:
1. Finished Dosage Form yes
2. Same lot numbers TB-047A
3.2.P.5.4 Batch Analysis
Certificate of Analysis for Finished Dosage Form yes
3.2.P.5.5 Characterization of Impurities
3.2.P.5.6 Justification of Specifications</td><td>☒</td></tr>
<tr><td>3.2.P.7</td><td>Container Closure System
1. Summary of Container/Closure System (if new resin, provide data) yes
2. Components Specification and Test Data yes
3. Packaging Configuration and Sizes
<table><tr><th>Material</th><th>Supplier</th><th>Manufacturer</th></tr><tr><td>Container, 16 oz. (b) (4) Clear Glass (b) (4) Round Container (b) (4)

Closure, 28mm (b) (4) White, (b) (4) Smooth Top Closure (b) (4)</td><td>(b) (4)</td><td>(b) (4)</td></tr></table>4. Container/Closure Testing yes
5. Source of supply and suppliers address yes</td><td>☒</td></tr>
<tr><td>3.2.P.8</td><td>3.2.P.8.1 Stability (Finished Dosage Form)
1. Stability Protocol submitted yes
2. Expiration Dating Period 24 month exp
3.2.P.8.2 Post-approval Stability and Conclusion
Post Approval Stability Protocol and Commitments yes
3.2.P.8.3 Stability Data
1. 3 month accelerated stability data yes
2. Batch numbers on stability records the same as the test batch yes:TB-047A</td><td>☒</td></tr>
</table>

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NA** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation yes Theoretical Yield see below Actual Yield see below Packaged Yield see below **3.2.R.1.P.2 Information on Components** yes **3.2.R.2.P Comparability Protocols** n/a **3.2.R.3.P Methods Validation Package** NA Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type:** (Continue with the appropriate study type box below)	☐

5.3.1.2 Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) ☒

Statistical Summary of the Comparative Bioavailability Data – Hydrocodone

Hydrocodone 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=30[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	158.11	160.46	98.54	(95.00, 102.20)
AUC_{0-inf}	161.38	163.45	98.73	(95.36, 102.23)
C_{max}	14.56	15.05	96.73	(93.12, 100.48)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	184.85	188.84	97.89	(93.61, 102.36)
AUC_{0-inf}	187.76	191.65	97.97	(93.74, 102.40)
C_{max}	14.85	14.85	99.95	(96.06, 104.00)

Statistical Summary of the Comparative Bioavailability Data – Chlorpheniramine

Chlorpheniramine 5 mL (1 x 5 mL) Geometric Means[1], Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data				
Fasted Bioequivalence Study (CRI-00014527/S08-0404/R09-0218) N=29[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	391.89	409.19	95.77	(91.25, 100.52)
AUC_{0-inf}	431.33	452.78	95.26	(90.41, 100.37)
C_{max}	12.21	12.99	93.99	(88.62, 99.69)
Fed Bioequivalence Study (CRI-00014528/S08-0405/R09-0219) N=28[2]				
Parameter	**Test**	**Reference**	**% Ratio**	**90% C.I.**
AUC_{0-t}	401.31	399.80	100.38	(95.24, 105.79)
AUC_{0-inf}	435.25	430.18	101.18	(96.25, 106.35)
C_{max}	11.55	11.62	99.45	(93.41, 105.88)

2. Summary Bioequivalence tables:
   Table 10. Study Information yes
   Table 12. Dropout Information yes
   Table 13. Protocol Deviations yes

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 11. Product Information yes
   Table 16. Composition of Meal Used in Fed Bioequivalence Study yes

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   Table 9. Reanalysis of Study Samples yes
   Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses yes
   Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples yes

5.3.7

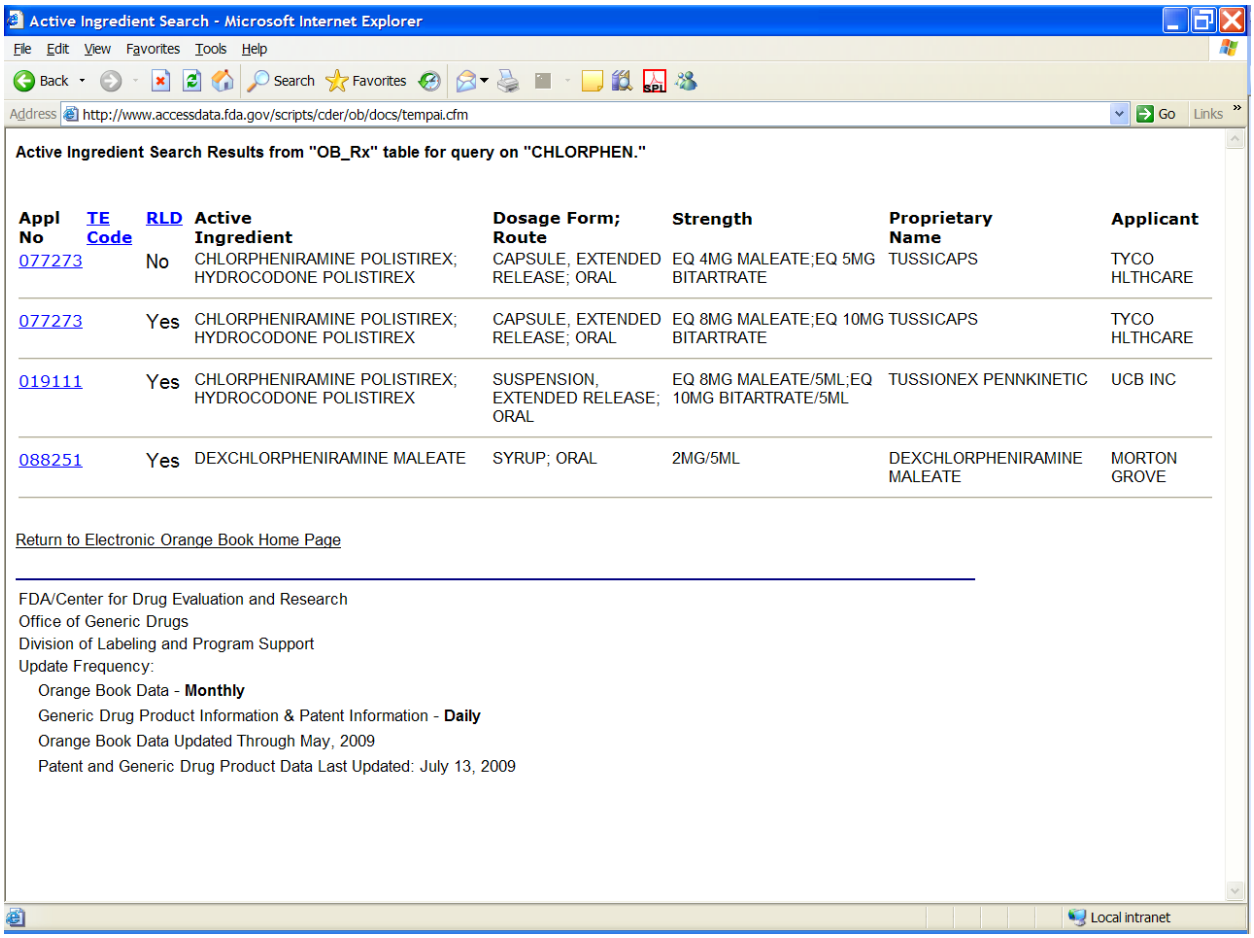
Case Report Forms and Individual Patient Listing yes

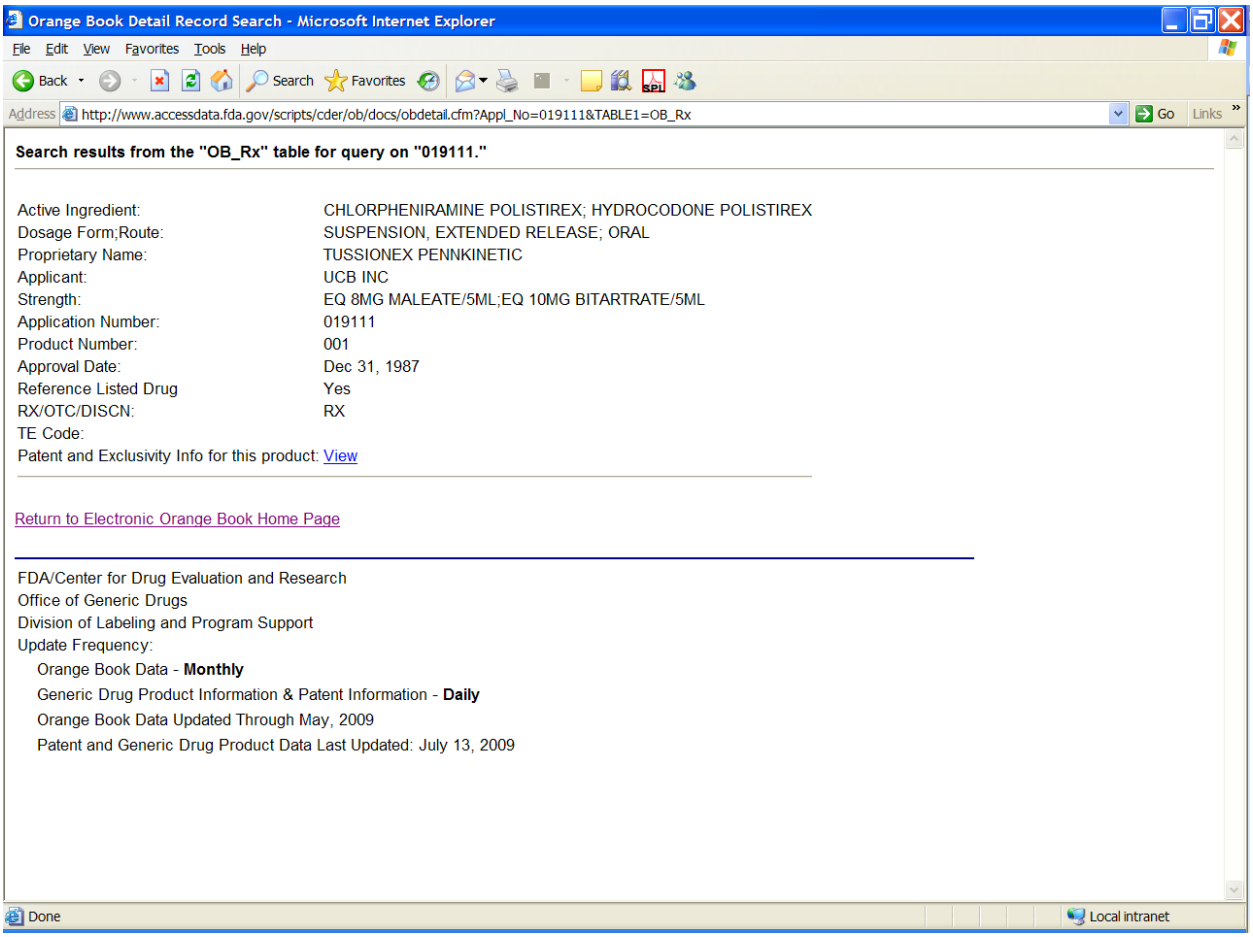
5.4	**Literature References**	☐

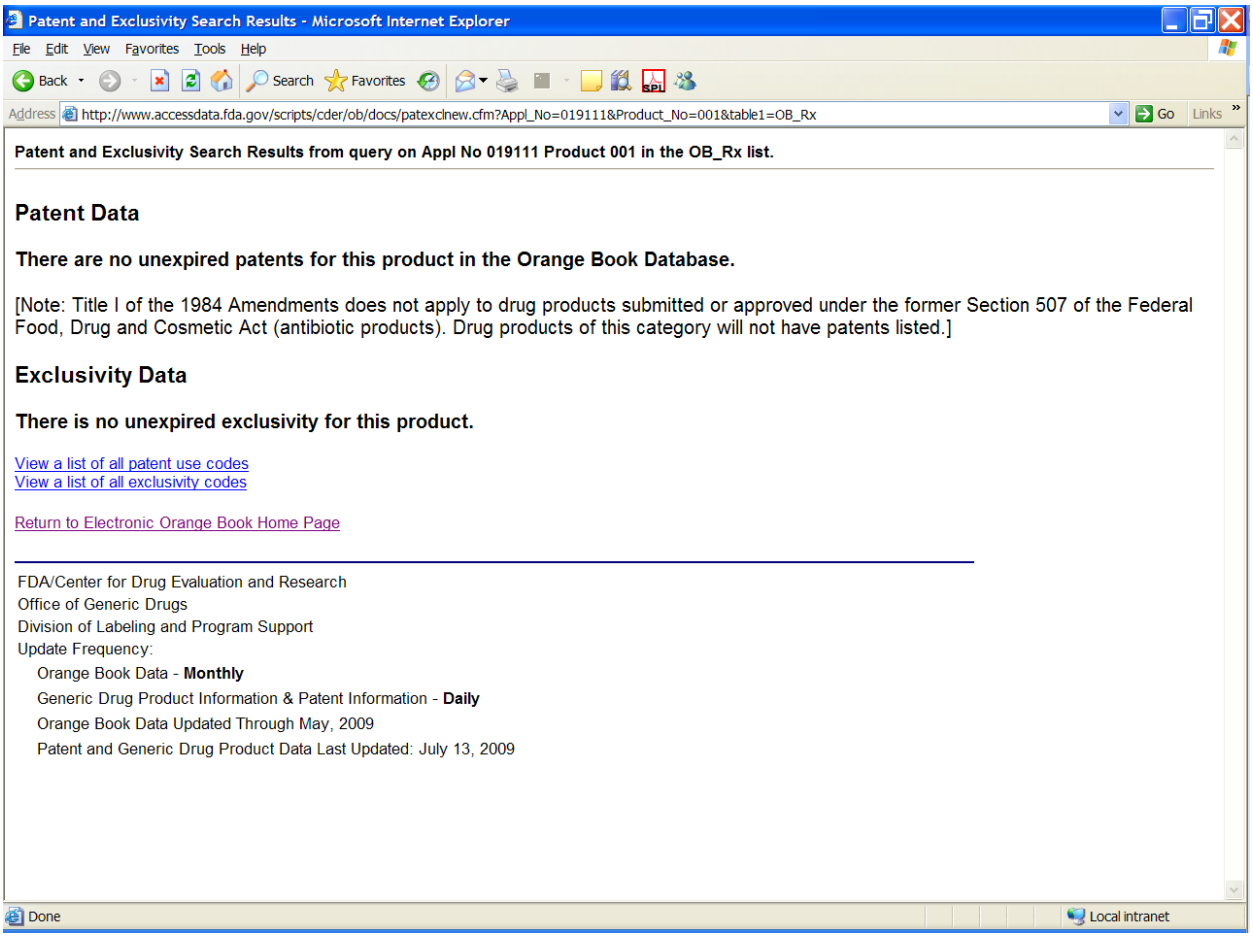
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 10MG AND 8 MG PER 5 ML 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)yes 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
Active Ingredient Search Results from "OB_Rx" table for query on "CHLORPHEN."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
077273 | | No | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | CAPSULE, EXTENDED RELEASE; ORAL | EQ 4MG MALEATE;EQ 5MG BITARTRATE | TUSSICAPS | TYCO HLTHCARE
077273 | | Yes | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | CAPSULE, EXTENDED RELEASE; ORAL | EQ 8MG MALEATE;EQ 10MG BITARTRATE | TUSSICAPS | TYCO HLTHCARE
019111 | | Yes | CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX | SUSPENSION, EXTENDED RELEASE; ORAL | EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML | TUSSIONEX PENNKINETIC | UCB INC
088251 | | Yes | DEXCHLORPHENIRAMINE MALEATE | SYRUP; ORAL | 2MG/5ML | DEXCHLORPHENIRAMINE MALEATE | MORTON GROVE
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 13, 2009
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=019111&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "019111."
Active Ingredient: CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX
Dosage Form;Route: SUSPENSION, EXTENDED RELEASE; ORAL
Proprietary Name: TUSSIONEX PENNKINETIC
Applicant: UCB INC
Strength: EQ 8MG MALEATE/5ML;EQ 10MG BITARTRATE/5ML
Application Number: 019111
Product Number: 001
Approval Date: Dec 31, 1987
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through May, 2009
Patent and Generic Drug Product Data Last Updated: July 13, 2009
Done
Local intranet



OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #91-632 **APPLICATION: TRIS PHARMA**
DATE OF SUBMISSION: 7/13/2009

DRUG: Chlorpheniramine Polistirex and Hydrocodone Polistirex Extended-Release Oral Suspension,10mg and 8mg Per 5 mL

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☐ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☐ Deny☐	
Micro Team Leader (sign as needed)	Grant☐ Deny☐	
Labeling Team Leader (sign as needed)	Grant☐ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☐ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: **SELECT TEAM # 4 Leigh Ann Bradford**
a) When expedited review is denied, notify the applicant by telephone

DATE

ENTER FORM INTO DFS

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/s/

FELECIA TAN
09/04/2009

MARTIN H Shimer
09/10/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-632

Tris Pharma, Inc.
Attention: W. Scott Groner
2033 Route 130
Monmouth Junction, NJ 08502

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated August 13, 2009 and your amendment dated August 26, 2009.

NAME OF DRUG: Chlorpheniramine Polistirex and Hydrocodone Polistirex
Extended-release Oral Suspension,
8 mg/5 mL and 10 mg/5 mL

DATE OF APPLICATION: July 13, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 27, 2009

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Leigh Ann Bradford
Project Manager
240-276-8453

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

FELECIA TAN
09/04/2009

MARTIN H Shimer
09/10/2009

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA/SUPPLEMENT #: 91-632
DRUG: Chlorpheniramine Polistirex and Hydrocodone Polistirex Oral Suspension
APPLICANT: Tris Pharma, Inc.
DATE OF SUBMISSION: August 27, 2009

The Office of Generic Drugs MaPP # 5240.1 lists the following criteria for granting expedited review status to a supplemental abbreviated new drug application. At least one of the criteria must be met.

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative

2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.

   a) Catastrophic events such as explosion, fire storms damage.

   b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:

      - Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
      - Relocation of a facility or change in an existing facility because of a catastrophic event (see item 2.a)

3. AGENCY NEED.
   a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
   b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
   c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
   d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	
Chemistry Team Leader (sign as needed)	Grant☒ Deny☐	
Micro Team Leader (sign as needed)	Grant☒ Deny☐	
Labeling Team Leader (sign as needed)	Grant☒ Deny☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant☒ Deny☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #

a) When expedited review is denied, notify the applicant by telephone

DATE

ENTER FORM INTO DFS

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/s/

FELECIA TAN
09/17/2009
Marty pls. reverify all is correct with the form :)

MARTIN H Shimer
09/18/2009

Labeling Comments

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773

TO: Tris Pharma, Inc.

TEL: 732-940-0358

ATTN: W. Scott Groner

FAX: 732-940-0374

FROM: Burhan Nour
burhan.nour@fda.hhs.gov
240-276-8990

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091632 Date of Submission: July 13, 2009

Applicant's Name: Tris Pharma, Inc.

Established Name: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended- Release Oral Suspension

Hydrocodone Polistirex equivalent to**10 mg** hydrocodone bitartrate and Chlorpheniramine Polistirex equivalent to **8 mg** chlorpheniramine maleate per 5 mL

Proprietary Name: None

Labeling Deficiencies:

A. CONTAINER (473 mL bottles)
Satisfactory in FPL as of July 13, 2009 e-submission

D. PACKAGE OUTSERT
HOW SUPPLIED: Clarify the strength in terms of hydrocodone bitartrate and chlorpheniramine maleate where referenced in this section.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

{See appended electronic signature page}

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN F GRACE
11/09/2009
for Wm Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 091632 Date of Submission: July 13, 2009

Applicant's Name: Tris Pharma, Inc.

Established Name: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended- Release Oral Suspension

Hydrocodone Polistirex equivalent to**10 mg** hydrocodone bitartrate and Chlorpheniramine Polistirex equivalent to **8 mg** chlorpheniramine maleate per 5 mL

Proposed Proprietary Name: None

Labeling Deficiencies:

A. CONTAINER (473 mL bottles)
Satisfactory in FPL as of July 13, 2009 e-submission

D. PACKAGE OUTSERT
HOW SUPPLIED: Clarify the strength in terms of hydrocodone bitartrate and chlorpheniramine maleate where referenced in this section.

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

BASIS OF APPROVAL:

APPROVAL SUMMARY

A. CONTAINER LABELS (Bottles of 473 mL)
Satisfactory in FPL as of July 13, 2009 e-submission

B. PACKAGE OUTSERT
Satisfactory in FPL as of (date) e-submission

Revisions needed post-approval:

REFRENCE LISTED DRUG
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Tussionex Pennkinetic Exended-release Oral Suspension
NDA Number: NDA 019111
NDA Drug Name: Tussionex Pennkinetic (Hydrocodone Polistirex and Chlorpheniramine Polistirex) Exended-release Suspension
NDA Firm: UCB, Inc.
Date of Approval of NDA Insert and supplement #: NDA 019111/S-015, approved March 11, 2008
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-side
Basis of Approval for the Package Outsert: side-by-side

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling for Tussionex® Pennkinetic® (hydrocodone polistirex/chlorpheniramine polistirex) Extended-Release Suspension (NDA 019111/S-015, approved March 11, 2008).

2. PATENTS/EXCLUSIVITIES

   There are no unexpired patents and exclusivities.

3. MANUFACTURING FACILITY

   Tris Pharma, Inc.
   2033 Route 130
   Monmouth Junction, NJ 08852

4. STORAGE CONDITIONS

   USP: None.
   RLD: Store at 15°-30°C (59°-86°F).
   ANDA: Store at 20° to 25°C (68°to 77°F); excursion permitted from 15° to 30°C (59°to 86°F) [See USP Controlled Room Temperature.]

5. DISPENSING RECOMMENDATIONS

   USP: None
   RLD: Dispense in a well-closed container.
   ANDA: Dispense in a well-closed container.

6. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling does appear accurate according to the components and composition statement.

Ingredients	Function	Quantity (mg/5 mL)
Sodium Polystyrene Sulfonate (b) (4)	(b) (4)	(b) (4)
Hydrocodone Bitartrate USP	Active	10
Chlorpheniramine Maleate USP	Active	8
Purified Water USP	(b) (4)	(b) (4)
Polyvinyl Acetate (b) (4)		
(b) (4)		
Triacetin USP		
Sodium Metabisulfite NF (b) (4)		
Polysorbate 80 NF (b) (4)		
Propylene Glycol USP		
Methylparaben NF		
Propylparaben NF		
Xanthan Gum NF (b) (4)		

Ascorbic Acid USP
Sodium Ascorbate USP
High Fructose Corn Syrup (b) (4)
(b) (4)
Sucrose NF
D&C Yellow No. 10
(b) (4) ood Starch – Modified)
(b) (4) Flavor (b) (4)
(b) (4)
(b) (4)

7. PACKAGING CONFIGURATIONS

RLD: Bottles of 473 mL
ANDA: Bottles of 473 mL

8. CONTAINER/CLOSURE

The drug product Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL test batch, TB-047A, was packaged in a 16 oz (473 mL) (b) (4) Clear Glass (b) (4) Round Container with smooth top closure.

Item	Description	Quantity per Unit	Comments
1	Clear, colorless to slightly yellow solution.	473 mL	--
2	Container, 16 oz. (b) (4) Clear Glass (b) (4) Round Container (b) (4)	1	--
3	Closure, 28mm (b) (4) White, (b) (4) Smooth Top Closure (b) (4)	1	--
4	Container Label	1	--
5	Outsert	1	On top of closure
6	Neck Band	1	--

9. PRODUCT DESCRIPTION

Hydrocodone Polistirex and Chlorpheniramine Polistirex ER Oral Suspension, 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL is described in the HOW SUPPLIED section as a yellow viscous suspension.

10. NAME & ADDRESS OF APPLICANT

Name:	Tris Pharma, Inc.
Address:	2033 Route 130 Monmouht Junction, NJ 08852
Representative:	W. Scott Groner Director, Regulatory Affairs and Compliance
Telephone:	Tel: (732) 940-0358
Fax:	Fax: (732) 940-0374

Date of Review: November 2, 2009

Date of Submission: July 13, 2009

Primary Reviewer: Burhan Nour

Team Leader: John Grace

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

BURHAN A NOUR
11/03/2009

JOHN F GRACE
11/09/2009

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

November 17, 2009

John F. Grace, Labeling Reviewer
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855
(240) 276-8420

Reference: ANDA 091632 Amendment, Sequence 0002
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Grace:

Reference is made to a Labeling Deficiency Letter received on November 09, 2009 from the Office of Generic Drugs concerning labeling deficiencies found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 a labeling amendment to the abbreviated new drug application, ANDA 091632, Sequence 0002, which includes a complete response to the deficiencies. Full details of the deficiencies and Tris responses are found in the attachment to this cover letter.

This eCTD is approximately 4.21 megabytes saved to a DVD disk. Symantec AntiVirus software, version 10.0.2.2000, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 2.03.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Labeling Deficiencies

A. CONTAINER (473 mL bottles)
Satisfactory in FPL as of July 13, 2009 e-submission

Response:

Tris acknowledges that the container label is satisfactory in FPL as of July 13, 2009 e-submission.

B. PACKAGE OUTSERT
HOW SUPPLIED: Clarify the strength in terms of hydrocodone bitartrate and chlorpheniramine maleate where referenced in this section.

Response:

A revised package outsert clarifying the strength in terms of hydrocodone bitartrate and chlorpheniramine maleate has been provided, refer to Module 1.14.2.2 for outsert layout, Module 1.14.2.3 for outsert in word, PDF and SPL format, and Module 1.14.3.1 for side-by-side comparison.

BIOEQUIVALENCE AMENDMENT

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Teresa Vu FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 13, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension Eq. 8 mg and 10 mg/5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request
Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 091632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have proposed the following dissolution testing method for your product:

   Apparatus: 2 (Paddle) at 50 rpm
   Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH not mentioned)
   Temperature: 37 ±0.5°C
   Sampling Time: 1, 3, 6 and 12 hours

   However, at the last sampling time point of 12 hours, your test product did not reach dissolution of at least 80% of either component, hydrocodone or chlorpheniramine. Please repeat the dissolution testing using your proposed method, and sample until at least 80% of both components is dissolved. Please also provide the pH of the medium after you add 400 mL of 0.27 M disodium phosphate to 495 mL of 0.1 N HCl.

2. In addition, please conduct dissolution testing using the following FDA-recommended method for the test and reference products for comparative evaluation of both methods:

   Medium: 495 mL Simulated Gastric Fluid (SGF) at 37°C
   Apparatus: USP 2 (Paddle) at 50 rpm
   Sampling Time: 1, 3, 8, 24 hours or until 80% of the each drug in the dosage form is dissolved

3. You have conducted dissolution testing in other media, viz., buffers at pH 1.2, 4.5 and 6.8. However, you have not provided the summary tables of dissolution data (testing date, mean dissolution, range, %CV, etc. for the test and reference products) in eCTD format. Please provide the summary tables. Additionally, the dissolution data on the individual dosage units are not legible. Please provide a legible copy of these dissolution testing results.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

DALE P CONNER
02/23/2010

QUALITY DEFICIENCY - MINOR

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Sarah Nguyen FDA CONTACT PHONE: (240)-276-8467

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 13, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension, 10 mg/5 mL and 8 mg/5 mL.

Reference is also made to your amendment dated August 26, 2009.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **4** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: 091632 APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-Release Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please provide [redacted] (b) (4)
2. Please comment [redacted] (b) (4)
3. Please provide [redacted] (b) (4)
4. [redacted] (b) (4)
5. [redacted]
6. [redacted]

7. [redacted] (b) (4)

8.

9.

10. Please add [redacted] (b) (4).

11. Please add [redacted] (b) (4).

12. [redacted] (b) (4).

13. Finished product release specification should include USP <467> residual solvents compliance statement along with option used.

14. Please revise [redacted] (b) (4).

15. Please explain [redacted] (b) (4).

16. [redacted] (b) (4)

17. [redacted] (b) (4)

18. Authorization letter to refer to [redacted] (b) (4). Please clarify.

19. Please add [redacted] (b) (4)

20. It is note in Module 3.2.P.8.1 that the containers were placed in the **horizontal position**; so that all sides of the container and the closure liner are in contact with the drug product. Please include the sample orientation in three months accelerated and on-going room temperature stability data. Also revise the stability protocol to include the orientation of stability samples.

21. [redacted] (b) (4)

22. Please clarify the storage condition of the following statement for "Expiration dating period" in Module 3.2.P.8.1. [redacted] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence section of your application is under review and you will be notified separately of any deficiencies.

2. A satisfactory compliance evaluation for each of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval.

3. Vendor qualification for reduced testing is a cGMP issue per 21 CFR211.84 and should be discussed with the field inspectors.

4. Please provide all available updated drug product controlled room temperature stability data for our evaluation.

Sincerely yours,

(See appended electronic signature page)

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

SHING HOU H LIU
02/25/2010
For Vilayat A. Sayeed, Ph.D.

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

March 04, 2010

Teresa Vu, Project Manager
Division of Bioequivalence
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855
(240) 276-8420

Reference: ANDA 091632 Amendment, Sequence 0003
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

- **Bioequivalence Response to Information Request**
- **Bioequivalence Dissolution Acknowledgement**

Dear Ms. Vu:

Reference is made to a Bioequivalence Deficiency Letter from the Office of Generic Drugs on February 23, 2010 concerning Bioequivalence Deficiency found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 a bioequivalence amendment to the abbreviated new drug application, ANDA 091632, Sequence 0003, which includes a complete response to the deficiencies. Full details of the deficiencies and Tris responses are found in the attachment to this cover letter.

This eCTD is approximately 4 megabytes saved to a DVD disk. Trend Micro Worry-Free Business Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from [redacted] (b) (4) in [redacted] (b) (4) eCentral, version 2.03.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the secure account e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Following this page, 2 pages withheld in full (b)(4)

Tris PHARMA

2033 ROUTE 130, SUITE D

MONMOUTH JUNCTION, NJ 08852

WWW.TRISPHARMA.COM

March 16, 2010

Sarah Nguyen
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855
(240) 276-8420

Reference: ANDA 091632 Amendment, Sequence 0004
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Nguyen:

Reference is made to a CMC Deficiency Letter from the Office of Generic Drugs on February 25, 2010 found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 a CMC amendment to the abbreviated new drug application, ANDA 091632, Sequence 0004, which includes a complete response to the deficiencies. Full details of the deficiencies and Tris responses are found in the attachment to this cover letter.

This eCTD is approximately 11.1 megabytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the secure account e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Following this page, 11 pages withheld in full (b)(4)

BIOEQUIVALENCE AMENDMENT

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Teresa Vu FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 13, 2009 and on March 4, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Polistirex and Chlorpheniramine Polistirex for Oral Suspension, 8 mg/5 mL and 10 mg/5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request
Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 091632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet.

Your proposed dissolution method is acceptable. However, based on the dissolution testing results, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5°C
Sampling Time: 1, 3, 6 and 12 hours
Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

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/s/

DALE P CONNER
04/19/2010

Tris PHARMA

2033 ROUTE 130, SUITE D

MONMOUTH JUNCTION, NJ 08852

WWW.TRISPHARMA.COM

April 28, 2010

Teresa Vu, Project Manager
Division of Bioequivalence
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Amendment, Sequence 0005
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Vu:

Reference is made to a Bioequivalence Letter from the Office of Generic Drugs on April 19, 2010 and telephone call on April 27, 2010 concerning a request to revise our proposed dissolution specification found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an amendment to the abbreviated new drug application, ANDA 091632, Sequence 0005, which includes duplicate test batch and R&D full scale trial batch data. **For review of current stability data on the Test Product, TB-047, see Sequence 0004 previously submitted.**

This eCTD is approximately 316 kilobytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the secure account e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

BIOEQUIVALENCE AMENDMENT

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Alpita Popat FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 13, 2009, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Polistirex and Chlorpheniramine Polistirex for Oral Suspension, 8 mg/5 mL and 10 mg/5 mL.

Reference is also made to your amendment dated March 4, 2010, April 26, 2010 and April 28, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA: 91632

APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Chlorpheniramine Polistirex and Hydrocodone Polistyrex ER Oral Suspension
Eq. 8 mg and 10 mg/5 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Based on the available dissolution data on fresh lots (Biobatch Lot # TB-047A, tested on 4/22-24/2009, 2/24/2010, and new batches Lot # RD-0286-001 and TB-071A), your proposed dissolution specifications are acceptable, except for hydrocodone at one-hour time point, and for chlorpheniramine at 3-hour time point. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:

Apparatus: 2 (Paddle) at 50 rpm
Media: 495 mL 0.1N HCI for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)
Temperature: 37 ±0.5°C
Sampling Time: 1, 3, 6 and 12 hours
Specifications:

TIME	HYDROCODONE	CHLORPHENIRAMINE
1 HR	(b) (4)	(b) (4)
3 HR		
6 HR		
12 HR		

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91632	ORIG-1	TRIS PHARMA INC	CHLORPHENIRAMINE POLISTIREX; HYDROCODONE POLISTIREX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALPITA POPAT
05/18/2010

DALE P CONNER
05/19/2010

Bioequivalence Dissolution Acknowledgement

Tris PHARMA

2033 ROUTE 130, SUITE D

MONMOUTH JUNCTION, NJ 08852

WWW.TRISPHARMA.COM

May 24, 2010

Teresa Vu, Project Manager
Division of Bioequivalence
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Amendment, Sequence 0006
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Vu:

Reference is made to a Bioequivalence Letter from the Office of Generic Drugs on May 19, 2010 concerning a request to revise our proposed dissolution specification found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an amendment to the abbreviated new drug application, ANDA 091632, Sequence 0006, which includes an acceptance of the specification as proposed by the agency. Full detail of this deficiency and the Tris response is found in the attachment to this cover letter.

Tris commits to submit a separate CMC Amendment within 1 week to the Division of Chemistry which shall include updated release and stability dissolution specifications.

This eCTD is approximately 350 kilobytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the secure account e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Deficiency and Response

Deficiency

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Based on the available dissolution data on fresh lots (Biobatch Lot # TB-047A, tested on 4/22-24/2009, 2/24/2010, and new batches Lot# RD-0286-001 and TB-071A), your proposed dissolution specifications are acceptable, except for hydrocodone at one-hour time point, and for chlorpheniramine at 3-hour time point. Please acknowledge your acceptance of the following recommended dissolution testing method and specifications:

Apparatus:	***2 (Paddle) at 50 rpm***
Media:	***495 mL 0.1N HCl for 1 hour, followed by addition of 400 mL of 0.27M Disodium Phosphate to obtain buffer solution (pH 6.8)***
Temperature:	***37ºC ± 0.5ºC***
Sampling Time:	***1, 3, 6 and 12 hours***
Specifications:	

Time	***Hydrocodone***	***Chlorpheniramine***
1HR	(b) (4)	(b) (4)
3HR		
6HR		
12HR		

Response:

Tris acknowledges that the review of the bioequivalence studies submitted has been completed. Tris has reviewed all available dissolution results and accepts the FDA–recommended method and specification for dissolution.

In addition, Tris upon completion of its Full-Scale Process Validation Batches may revisit the recommended specification for Hydrocodone at the 1 hour time point.

Tris PHARMA

2033 ROUTE 130, SUITE D

MONMOUTH JUNCTION, NJ 08852

WWW.TRISPHARMA.COM

May 25, 2010

Sarah Nguyen, Project Manager
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 CMC-Amendment, Sequence 0007
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Nguyen:

Reference is made to a Bioequivalence Letter from the Office of Generic Drugs on May 19, 2010 concerning a request to revise our proposed dissolution specification found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632. Tris has submitted a Bioequivalence amendment on May 24, 2010 accepting the FDA-recommended dissolution specification.

Tris submits today, in accordance with 21 CFR 314.96, a CMC amendment to the abbreviated new drug application, ANDA 091135, Sequence 0007, which includes the updated release specification (3.2.P.5.1), and updated stability specification (3.2.P.8.2).

This eCTD is approximately 400 kilobytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the secure account e-mail address is *reg.affairs@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Tris PHARMA

2033 ROUTE 130, SUITE D

MONMOUTH JUNCTION, NJ 08852

WWW.TRISPHARMA.COM

July 1, 2010

Sarah Nguyen, Project Manager
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Telephone CMC-Amendment, Sequence 0008
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Ms. Nguyen:

Reference is made to a telephone deficiencies received from the Office of Generic Drugs on June 28, 2010 found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 a CMC amendment to the abbreviated new drug application, ANDA 091632, Sequence 0008, which includes a complete response to the deficiencies. Full details of the telephone deficiencies and Tris responses are found in the attachment to this cover letter.

This eCTD is approximately 2 megabytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the *secure account e-mail address* is *TrisRA@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

July 19, 2010

Gil Keng
Office of Generic Drugs
CDER/FDA (HFD-600)
Electronic Document Room E-150
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Telephone (CMC) Amendment, Sequence 0009
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Keng:

Reference is made to a telephone deficiencies received from the Office of Generic Drugs on July 08, 2010 found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 a CMC amendment to the abbreviated new drug application, ANDA 091632, Sequence 0009, which includes a complete response to the telephone-deficiencies regarding 10-keto hydrocodone degradant. Full details of the telephone deficiencies and responses are found in the attachment to this cover letter.

This eCTD is approximately 3 megabytes saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this ANDA amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the *secure account e-mail address* is *TrisRA@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

September 10, 2010

Gil Keng, CMC Reviewer
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Telephone Amendment, Sequence 0010
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Keng:

Reference is made to a **telephone deficiencies** received from the Office of Generic Drugs on September 9, 2010 found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an amendment to the abbreviated new drug application, ANDA 091632, Sequence 0010, which includes a complete response to the telephone-deficiencies. Full details of the telephone deficiencies and responses are found in the attachment to this cover letter.

This eCTD is approximately 500 KB saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the *secure account e-mail address* is *TrisRA@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

September 14, 2010

Gil Keng, CMC Reviewer
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Telephone Amendment, Sequence 0011
Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Keng:

Reference is made to a **telephone deficiency** received from the Office of Generic Drugs on September 14, 2010 regarding particle size testing for finished product, found upon review of the ANDA submission for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL, ANDA 091632.

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an amendment to the abbreviated new drug application, ANDA 091632, Sequence 0011, which includes a complete response to the telephone-deficiencies. Full details of the telephone deficiency and response are found in the attachment to this cover letter.

This eCTD is approximately 400 KB saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the *secure account e-mail address* is *TrisRA@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

Following this page, 1 page withheld in full (b)(4)

TELEPHONE CONFERENCE FAX

ANDA 091632

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Tris Pharma, Inc. TEL: (732) 940-0358

ATTN: W. Scott Groner FAX: (732) 940-0374

FROM: Sarah Nguyen FDA CONTACT PHONE: (240) 276-8467

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 13, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Hydrocodone Polistirex and Chlorpheniramine Polistirex for Oral Suspension, 10 mg/5 mL and 8 mg/5 mL.

The deficiencies presented below represent TELEPHONE deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Sarah Nguyen at (240)-276-8467. Please submit documentation by fax to the attention of the Project Manager at (240) 276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

*After the effective date, **01-Aug-2010**, ANDAs will only be accepted at the new mailing address listed above. **DO NOT submit your ANDA Regulatory documents to this address prior to 01-Aug-2010.** For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/*

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 091632 APPLICANT: Tris Pharma, Inc.

DRUG PRODUCT: Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension, eq. to 10 mg hydrocodone bitartrate and 8 mg chlorpheniramine maleate per 5 mL

The deficiencies presented below represent TELEPHONE deficiencies.

A. Deficiencies:

1. Please establish (b) (4)

2. (b) (4)

3. Please establish (b) (4) .

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Please provide all available updated drug product controlled room temperature stability data for our evaluation.

Sincerely yours,

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GIL JONG KANG
09/20/2010

Tris PHARMA

2033 ROUTE 130, SUITE D
MONMOUTH JUNCTION, NJ 08852
WWW.TRISPHARMA.COM

September 24, 2010

Gil Kang, CMC Reviewer
Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

Reference: ANDA 091632 Telephone Amendment, Sequence 0012

Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL

Dear Mr. Kang:

Tris Pharma, Inc. (Tris) submits today, in accordance with 21 CFR 314.94 an **telephone amendment** to the ANDA 091632, Sequence 0012, which includes a complete response to the CMC Reviewer Gil Kang from the Office of Generic Drugs on September 23, 2010 for Hydrocodone Polistirex & Chlorpheniramine Polistirex ER Oral Suspension, eq. to 10 mg hydrocodone bitartrate & 8 mg chlorpheniramine maleate per 5 mL.

1. Tris commits post approval to manufacture (b) (4)
2. (b) (4)

This eCTD is approximately 500 KB saved to a DVD disk. Trend Micro Security Standard AntiVirus software, version 6.0 service pack 1, was utilized to ensure that the submission is virus free. The submission was formatted with eCTD software purchased from (b) (4) in (b) (4) eCentral, version 3.0.

Please forward any written communications regarding this amendment to the undersigned. Feel free to call (732) 940-0358 or fax (732) 940-0374 to Tris Regulatory Affairs. For your convenience the *secure account e-mail address* is *TrisRA@trispharma.com*

Sincerely,

W. Scott Groner
Director Regulatory Affairs and Compliance

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: III	Team: 4	PM: Sarah Nguyen

Electronic ANDA: Yes ☒ No ☐

ANDA #:91632
Firm Name:Tris Pharma, Inc.
ANDA Name:Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended Release Oral Suspension, 10 mg and 8 mg/5 mL
RLD Name:Tussionex Pennkinetic; UCB Inc.; 19111

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 4\Electronic AP Summary\ 91632 AP_ROUT_SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 4\Final Version For DARRTS Folder\APTA letters\ 91632 AP_ltr .doc

Project Manager Evaluation: **Date: 7/21/10 Initials:** SN

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date n/a

Original Rec'd date 7/14/09	Date of Application 7/13/09	Date Acceptable for Filing 8/26/09
Patent Certification (type) II	Date Patent/Excl. expires	Citizens' Petition/Legal Case? Yes☐ No ☐ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** (b) (4) (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☒ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 5/14/10* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 8/10/10 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 6/29/10 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/30/09 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☐; Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☒ No ☐ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☒ No ☐ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 8/10/10 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: n/a

☐ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐ Filed AP Routing Summary in DARRTs	☐ Notified Firm and Faxed Copy of Approval Letter	☐ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 9/30/10**

Chief, Reg. Support Branch **Initials:** rlw/for

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD =Tussionex NDA#19-111 Date Checked N/A Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days:Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 7/14/2009, BOS=Tussionex Pennkinetic NDA 19-111, PII certification provided. RTR issued on 8/13/2009. ANDA ack for filing on 8/27/2009 (LO dated 9/10/2009). There are no remaining unexpired patents or exclusivities which protect the RLD. This ANDA is eligible for immediate Full Approval.	

2. ***Labeling Endorsement***

Reviewer, Burhan Nour:
Date8/10/10
InitialsBN

Labeling Team Leader, John Grace:
Date8/11/10
InitialsJG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:

From: Grace, John F
Sent: Wednesday, August 11, 2010 2:34 PM
To: Nour, Burhan
Subject: RE: labeling sign-off for ANDA 91632; Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, 10 mg and 8 mg/5mL; Tris Pharma, Inc.

concur.

From: Nour, Burhan
Sent: Wednesday, August 11, 2010 2:33 PM
To: Grace, John F
Subject: FW: labeling sign-off for ANDA 91632; Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, 10 mg and 8 mg/5mL; Tris Pharma, Inc.

From: Nour, Burhan
Sent: Tuesday, August 10, 2010 8:54 AM
To: Nguyen, Sarah; Grace, John F

Subject: RE: labeling sign-off for ANDA 91632; Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, 10 mg and 8 mg/5mL; Tris Pharma, Inc.

John,

There are no changes or updates.

Burhan

From: Nguyen, Sarah
Sent: Tuesday, August 10, 2010 8:26 AM
To: Nour, Burhan; Grace, John F
Subject: labeling sign-off for ANDA 91632; Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, 10 mg and 8 mg/5mL; Tris Pharma, Inc.

Please conduct labeling sign-off for ANDA 91632; Hydrocodone Polistirex and Chlorpheniramine Polistirex Extended-release Oral Suspension, 10 mg and 8 mg/5mL; Tris Pharma, Inc.
<< File: 91632_AP_ltr.doc >> << File: 091632ap1[1].pdf >>
Thanks,
Sarah

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 9/30/10**
OGD Regulatory Counsel **Initials rlw/for**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:N/A. There are no patents currently listed in the "Orange Book" for this drug product.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 9/15/10**
Chemistry Div. **III (Sayeed)** **InitialsDSG**
Comments:cmc acceptable

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 10/1/10**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
With his endorsement of the CMC section of this ANDA, the chemistry division director has concurred that there are no precident setting issues associated with the review and approval of this ANDA. Thus, further CMC review is not needed.

OGD Office Management Evaluation

6. Peter Rickman **Date 9/30/10**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) found acceptable. In-vitro dissolution, as amended, also found acceptable. DSI inspection (routine) requested for clinical site under NDA (b) (4). The inspection was completed and found acceptable. Office-level bio endorsed 2/4/10, 4/15/10, 5/18/10, 5/28/10 (dissolution) and 6/29/10 (DSI inspectional status).

Final-printed labeling (FPL) found acceptable for approval 11/30/09, as endorsed 8/11/10.

AND/OR

7. Robert L. West **Date 10/1/10**
Deputy Director, OGD **Initials RLWest**
Para.IV Patent Cert: Yes☐ No☒
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 5/14/10 (Verified 9/30/10). No "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS
Comments: RLWest for Keith Webber, Ph.D. 10/1/10.
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date 10/1/10
Initials RG for SN

Check Communication and Routing Summary into DARRTS

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 019111 Product 001 in the OB_Rx list.

<>

There are no unexpired patents for this product in the Orange Book Database.

<>

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through August, 2010
Patent and Generic Drug Product Data Last Updated: September 30, 2010

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- Web Site Policies
- FOIA
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- No FEAR Act

- Combination Products
- Advisory Committees
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- State & Local Officials
- Consumers
- Industry
- Health Professionals

-
-

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T GAINES
10/01/2010